FORMULATION AND DEVELOPMENT OF EXTENDED RELEASE DOSAGE FORM OF AN ANTICONVULSANT DRUG

DISSERTATION

Submitted to

THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI-32

In partial fulfillment of the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

OCTOBER 2016

PADMAVATHI COLLEGE OF PHARMACY AND RESEARCH INSTITUTE

Periyanahalli, krishnagiri Main Road,

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CERTIFICATE

This is to certify that the dissertation entitled **"FORMULATION AND DEVELOPMENT OF EXTENDED RELEASE DOSAGE FORM OF AN ANTI-CONVULSANT DRUG"** was carried out by **Mohamed Rafi. A** (Reg. No: 261410854), under the guidance of **Dr.R.P.Ezhilmuthu,M.Pharm, Ph.D., Professor & Head** in the Department of Pharmaceutics, Padmavathi College of Pharmacy and Research Institute, Dharmapuri, Affiliated to The Tamilnadu Dr. M.G.R Medical University, Chennai - 32.

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Dr. R.P.Ezhilmuthu, M.Pharm,Ph.D.,

Place: Dharmapuri

Date:

DECLARATION

I hereby declare that the matter embodied in the dissertation entitled **"FORMULATION AND DEVELOPMENT OF EXTENDED RELEASE DOSAGE FORM OF AN ANTI-CONVULSANT DRUG"** is a bonafide and genuine research work carried by us under the guidance of **Dr. R.P.Ezhilmuthu, M.Pharm., Ph.D.,** Professor & Head, Department of Pharmaceutics, Padmavathi College of Pharmacy & Research Institute, Periyanahalli, Dharmapuri.

MOHAMED RAFI. A **REG.NO:(261410854)**

Place: Dharmapuri

Date:

EVALUATION CERTIFICATE

This is to certify that the work embodied in this thesis entitled "**FORMULATION AND DEVELOPMENT OF EXTENDED RELEASE DOSAGE FORM OF AN ANTICONVULSANT DRUG"** submitted to the **Tamil Nadu Dr. M.G.R. Medical University**, was carried out by **MOHAMED RAFI. A (Reg.No: 261410854)** in the partial fulfillment of the Degree of **"Master of Pharmacy" in Pharmaceutics** under the supervision of D**r.R.P.EZHILMUTHU, M.Pharm**,Ph.D., Professor and Head, Department of Pharmaceutics, Padmavathi College of Pharmacy & Research Institute, Dharmapuri.

This work is original and has not been submitted in part or full for the award of any other degree or diploma of any other University.

Internal Examiner **External Examiner**

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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
HPMC	Hydroxy propyl Methylcellulose
CMC Sodium	Carboxy methyl Cellulose Sodium
IR Graph	Infra-Red Graph
ppm	Parts per million
RMG	Rapid Mixer Granulator
USP	United States Pharmacoepia
% RH	Percentage Relative Humidity
% RSD	Percentage Relative Standard Deviation
ICH	International Conference for Harmonization
RPM	Revolutions per minute
nm	Nano meters
µg	Microgram
mg	Milligram
gm	Gram
µm	Micrometer
cm	Centimetre
hrs.	Hours
Fig	Figure
%	Percentage
pH	Hydrogen ion concentration
E R	Extended Release
°C	Degree Celsius
FT-IR	Fourier Transform Infra Red Spectroscopy
UV	Ultra Violet spectroscopy
R^2	Regression coefficient
T½	Elimination half life
n	Slope constant
HPLC	High Performance Liquid Chromatography

ACKNOWLEDGEMENT

I thank the God's Almighty for his blessings on the accomplishment of this venture.

The task of preparing this dissertation has been fascinating experience and it is really a moment of great pleasure for me to express my hearty gratitude to those who have helped me in success full completion of this dissertation.

I take it as a privilege in tendering my deep sense of gratitude and indebtedness to my guide **Dr. R.P. Ezhil Muthu, M.Pharm, Ph.D., Head, Department of Pharmaceutics,** Padmavathi College of Pharmacy & Research Institute for his excellent suggestions, in valuable guidance, constant inspiration and sustained interest throughout my work

I would like to express my sincere thanks to our principal, **Dr. D.C.Prem Anand, M. Pharm., Ph.D.,** Padmavathi College of Pharmacy & Research Institute for her kind co-operation and encouragement and for providing us with all facilities required to proceed with my study.

My sincere and warm thanks to our **Kalvi Kodai Vallal Mr. M.G.Sekhar, B.A.,B.L., Ex.M.L.A.,**Chairman,Sapthagiri,Padmavathi & Pee Gee Group of institutions for granting me permission to utilize all the facilities and amenities to successfully achieve this task.

I am very much thankful to **Dr. M.Muthukumaran, M.Pharm., Ph.D.,Professor, Mrs. T.Usha, M.Pharm., Asst. Professor, Prof.Mr.Mohanasubramaniam, Department of Pharmaceutics** for his valuable help during my project work.

I express my Sincere thanks to **Mr. Saravanan, M.Pharm, (Ph.D)., Professor, Department of Analysis** for her valuable suggestions and inspiration.

I also express my sincere thanks to **Mr. V.Palanivel, M.Pharm, Ph.D., Mr.Paneer Selvam, M.Pharm., Mrs. Gomathi, M.Pharm., Department of Pharmacology** for his valuable suggestions.

I also express my sincere thanks to **Prof. Raja, M.Pharm, Mrs.V.Ganambaigai, M.Pharm., Department of Pharmacognosy** for his valuable suggestions.

I also express my sincere thanks to **Mr. Immanual, M.Pharm, Mrs.Lavanya, M.Pharm., Department of Pharmacy Practice** for his valuable suggestions.

I also express my sincere thanks to **Mrs.B.E.Rohini, M.Pharm., Department of Pharmaceutical Chemistry** for his valuable suggestions.

My sincere thanks to **Non teaching staff** for their valuable suggestions and support in completion of my project.

I express my sincere thanks to our friends for their support and help during the work.

Words are not sufficient to express my deepest love and appreciation to my affectionate to my beloved Parents who extended great support, love and care towards me during this great time.

Sincere thanks to all

MOHAMED RAFI.A **(261410854)**

1. INTRODUCTION

The ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site(s) of action is attained immediately and is then maintained constant for the desired duration of the treatment. If the provided dose size and frequency of administration are correct, therapeutic steady state plasma concentration of a drug can be achieved promptly and maintained by the respective administration of conventional peroral dosage forms. However there are number of potential limitations associated with this. These limitations are:

- The concentration of drug in the plasma and hence at the site(s) of action of the drug fluctuates over successive dosing intervals, even when the so-called 'Steady-state condition' is achieved. Hence it is not possible to maintain a therapeutic concentration of drug which remains constant at the site(s) of action for the duration of treatment.
- The inevitable fluctuations of steady-state concentrations of drug in the plasma and hence at the site(s) of action can lead to a patient being over or under medicated.
- For drugs with short biological half-lives frequent doses are required to maintain steady state plasma concentrations within the therapeutic range. For such drugs, the maintenance of therapeutic plasma concentrations is particularly susceptible to the consequence of forgotten doses and the overnight no-dose period.
- Lack of patient compliance, which is more likely in the case of regimens requiring frequent administration of conventional dosage forms.

These limitations and requirements led pharmaceutical scientists to consider presenting therapeutically active molecules in 'extended release' preparations.

Over the years, there has been an enormous amount of work put into designing drug delivery systems that can eliminate or reduce the cyclical plasma concentrations seen after conventional drug delivery systems are administered to a specified dosage regimen.

A variety of terms were used to describe these systems.

- **Delayed release products**

  Delayed release indicates that the drug is not being released immediately following administration but at a later time.

  E.g., Enteric coated tablets, Pulsatile-release capsules.

- **Repeat action products**

  Repeat action indicates that an individual dose is release fairly soon after administration and second or third doses are subsequently released at intermittent intervals.

- **Prolonged release products**

  Prolonged release indicates that the drug is provided for absorption over a longer period of time than from a conventional dosage form. However there is an implication that onset is delayed because of an overall slower release rate from the dosage form.

- **Sustained release products**

  Sustained release indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration and then a gradual release over an extended period.

Extended release products (ER)

Extended release dosage forms release drug slowly, so that plasma concentrations are maintained at a therapeutic level for a prolonged period of time (usually between 8 and 12 hours).

Controlled release (CR)

Controlled release dosage forms release drug at a constant rate and provide plasma concentrations that remain invariant with time.

Modified release products

Modified release dosage forms are defined by the USP in those whose drug release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms.

It is interesting to note that the USP considers that the terms controlled release, prolonged release and sustained release are interchangeable with extended release.

Extended release dosage form allows a twofold reduction in dosing frequency or increase in patient compliance or therapeutic performance.

The development of the oral controlled release system has been a challenge to formulation scientists due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract. Matrix type drug delivery systems as carriers for the active ingredients are interesting and promising option in developing an oral controlled release system.

SUSTAINED RELEASE DOSAGE FORMS

Conventional drug products like tablets and capsules are formulated to release the active drug immediately to obtain rapid and complete systemic absorption of the drug. The conventional dosage form maintains the constant plasma drug concentration for the long period of time by administering in a particular dose and at particular frequency. The frequency of administration or the dosing interval of any drug depends upon its half-life or mean residence time (MRT) and its therapeutic index. In most cases, the dosing interval is much shorter than the half-life of the drug resulting in a number of limitations. These limitations can overcome by formulating into Modified-Release dosage forms. Modified-release products provide either delayed-release or extended-release of the drug.

The terms sustained release, prolonged release or extended release are used to identify drug delivery systems that are designed to achieve a prolonged therapeutic blood or tissue levels of the drug by continuous releasing of the medication for an extended period of time after administration of a single dose.

The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using novel drug delivery systems and to promote therapeutic benefits while at the same time minimizing toxic effect. Extended release tablets and capsules are commonly taken only once or twice daily. Typically extended-release products provide an immediate release of drug which promptly produces the desired therapeutic effect which then is followed by gradual and continual release of additional amounts of drug to maintain this effect over a predetermined period of time. The sustained plasma drug levels provided by extended-

release drug products often eliminates the need for night dosing, which provides benefit to the patient.

Advantages of Extended-Release System

- Reduction in drug blood level fluctuations
- Frequency reduction in dosing
- Enhanced patient convenience and compliance
- Reduction in adverse side effects
- Reduction in overall health care costs

Disadvantages

- Loss of flexibility in adjusting the drug dose and/or dosage regimen.
- Increased risk of sudden and total drug release or dose dumping due to failure of technology of the dosage unit.

Drug candidates suited for extended release dosage forms

The drug and the therapeutic indication must be considered jointly in determining whether or not to develop an extended release dosage form.

For a successful extended release product, drug must be released from the dosage form at a predetermined rate, dissolve in the gastrointestinal fluids, maintain sufficient gastrointestinal residence time and be absorbed at a rate that will replace the amount of drug being metabolized and excreted.

- Drugs having short-biological half lives
- Drugs with fairly rapid rate of absorption and excretion
- Drugs which are uniformly absorbed in gastrointestinal tract.
- Drugs which require relatively smaller dosage for therapeutic effect.
- Drugs which are used for chronic rather than acute condition.

- Drugs which are having good margin of safety. The most widely used measure of the margin of a drug's safety is its therapeutic index. The larger the therapeutic index, the safer the drug.

Rationale for extended release dosage forms

- Many drugs are not inherently long lasting and require multiple daily dosing to achieve the desired therapeutic results.

  Multiple daily dosing often is inconvenient for patient and can result in missed doses, made up doses and patient non-compliance with therapeutic regimen.

- Extended release tablets and capsules are commonly taken only once or twice daily compared with counterpart conventional forms that may need to be taken three or four times daily to achieve the same therapeutic effect.

- Extended release products provide an immediate release of the drug that promptly produces the desired therapeutic effect, which is then followed by the gradual and continual release of additional amount of drug to maintain this effect over a predetermined period of time.

- The sustained plasma drug levels provided by extended release drug products often times eliminate the need for right dosing that provides benefit not only to the patient but to the caregiver as well.

Classification of extended release products

Extended release tablets are often classified according to the mechanism of drug release. The following are the most common means used to achieve a slow, control release of drug from tablets.

- Dissolution control
- Diffusion control
- Dissolution and diffusion control
- Erosion control
- Osmotic pump control & Ion exchange control

Dissolution controlled Release system

Most of the products fall into two categories

(a)Encapsulation dissolution controlled systems

Here the drug particles are coated or encapsulated by one of the several microencapsulation techniques with slowly dissolving materials like cellulose, PEGs, polymethacrylates, waxes, etc. The resulting pellets may be filled as such in hard gelatin capsules (popularly called as spansules) or compressed into tablets. The dissolution rate of coat depends upon the solubility and thickness of the coating which may range from 1 to 200 microns.

(b)Matrix dissolution controlled systems

Matrix systems are also called as monoliths since the drug is homogeneously dispersed throughout a rate-controlling medium. They are very common and employ waxes such as beeswax, carnauba wax, hydrogenated castor oil, etc. which control drug dissolution by controlling the rate of dissolution fluid penetration into the matrix by altering the porosity of tablet, decreasing its wettability or by itself getting dissolved at a slower rate. The wax embedded drug is generally prepared by dispersing the drug in molten wax and congealing and granulating the same. The drug release is often first-order from such matrices.

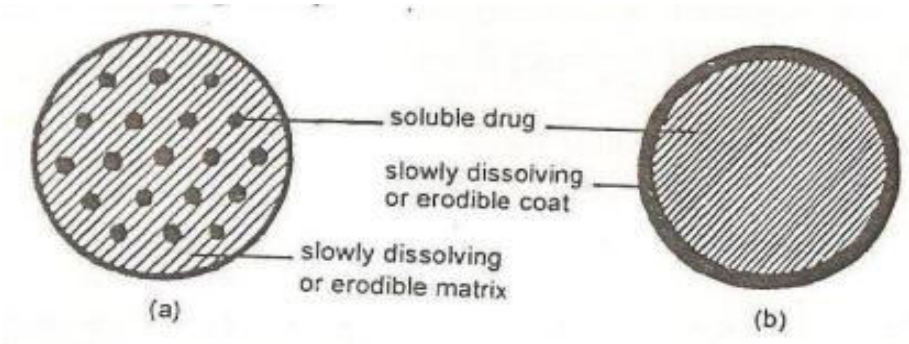


Fig.1 Dissolution Controlled Release Systems

a) Matrix system b) Coated/Encapsulated System

Diffusion controlled Release systems

Diffusion of a drug molecule provides the movement from a zone of high concentration to that of low concentration. Here, the formulator relies on the diffusion of the drug through an inert membrane barrier to control the release rate of a drug. The drug release rate is never zero-order since the diffusional path length increases with time as the insoluble matrix is gradually depleted of drug.

The two types of diffusion controlled systems.

(a)Matrix diffusion controlled systems

The drug is dispersed in an insoluble matrix of rigid non-swellable hydrophobic materials or swellable hydrophilic substances. Materials used for rigid matrix are insoluble plastics such as PVC and fatty materials like stearic acid, bees wax, etc.

Swellable matrix systems are popular for sustaining the release of highly water-soluble drugs. The material for such matrices are generally hydrophilic gums and may be of natural origin (Guar gum, Tracaganth), semi synthetic (HPMC,CMC, Xanthan gum) or synthetic (Poly acrylamides)

The release of drug from such matrix systems involve simultaneous absorption of water (resulting in hydration, gelling and swelling of gum) and desorption of drug

via a swelling controlled diffusion mechanism. As the gum swells and the drug diffuses out of it, the swollen mass, devoid of drug appears transparent.

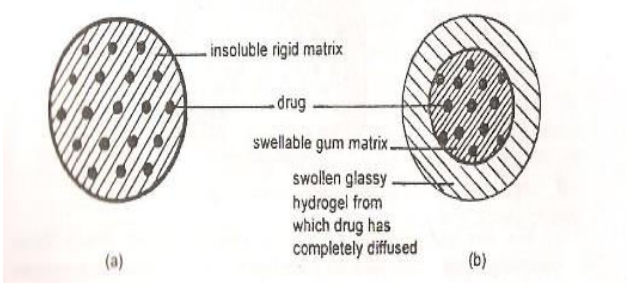


Fig.2 Diffusion Controlled Systems

a) Rigid matrix b) Swellable matrix

(b)Reservoir diffusion controlled systems

These systems are hollow containing an inner core of drug surrounded in a water &insoluble polymer membrane. The polymer can be applied by coating or microencapsulation techniques. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion. The polymers commonly used in such devices are HPC, Ethyl cellulose and polyvinyl acetate.

A disadvantage of all such microencapsulated drug release systems is a chance of sudden drug dumping which is not common with matrix devices.

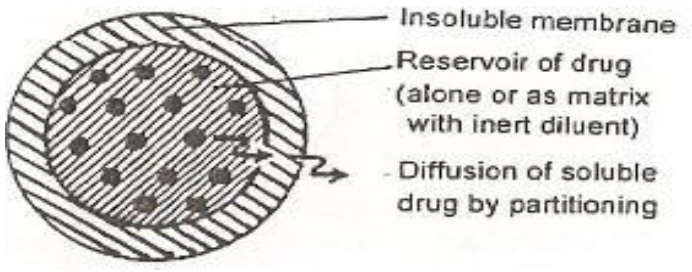


Fig.3 Drug release by diffusion across the insoluble membrane

Dissolution and diffusion controlled release systems

A combined dissolution and diffusion control of drug release can be accomplished by coating a drug core with a partially soluble membrane.Usually this membrane contains a combination of hydrophobic and hydrophilic polymers.

Eg. a mixture of ethyl cellulose and pvp.

The dissolution of the hydrophilic polymer causes the formation of pores through the membrane

-Permit the entry of aq. medium into the core and hence drug dissolution

-Allow diffusion of dissolved drug out of the system

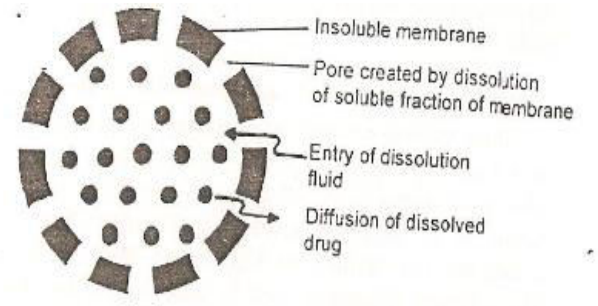
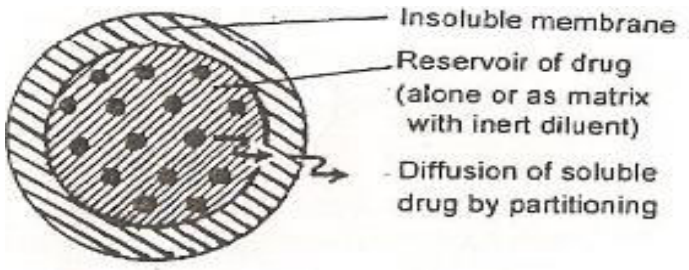


Fig.4 Dissolution and Diffusion Controlled Release System



Formulation of extended release system

There are three main classes of delivery system

- Monolithic or matrix systems
- Reservoir or membrane controlled systems
- Osmotic pump systems.

There is a basic principle that governs all these systems. In a solution drug diffusion will occur from a region of high concentration to a region of low concentration. This concentration difference is the driving force of drug diffusion out of the system [8].

Components of extended release delivery system

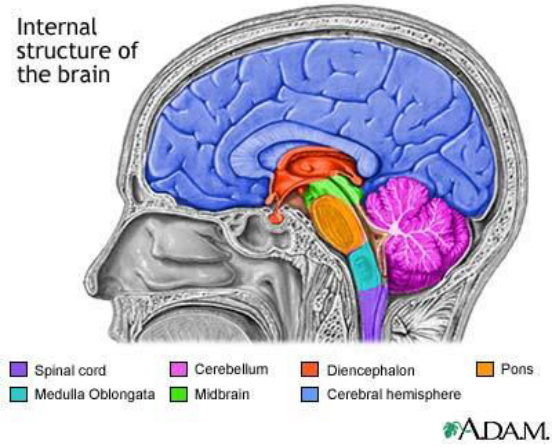
These include

- Active drug
- Release controlling agents (matrix formers, membrane formers)
- Matrix or membrane modifier, such as channeling agents for wax matrices and solublisers/and wicking agents for hydrophilic matrices
- Solubiliser, pH modifier and density modifier
- Lubricant and flow aid
- Density modifiers (if any)

EPILEPSY

- Epilepsy is a neurological disorder characterized by unprovoked, recurring seizures that disrupt the nervous system and can cause mental and physical dysfunction.
- The structures of the brain include the spinal cord, the brainstem, consisting of the medulla oblongata, the pons and the midbrain; the cerebellum; the cerebrum (one half, or hemisphere shown); and the diencephalon.

Fig 5: Internal structure of brain



- Criteria for Classifying Epilepsies and Seizures
- Seizures are a symptom of epilepsy. Epilepsy types are generally put into two categories, which are based on the specific biologic mechanisms involved in the seizure and the anatomical location of the seizure. The two types are:
- ***Partial (also called focal or localized) seizures****:* These seizures are more common than generalized seizures and occur in one or more specific locations in the brain. In some cases, partial seizures can spread to wide regions of the brain. They are likely to develop from specific injuries, but in most cases the exact origins are unknown.
- ***Generalized seizures****:*These seizures typically occur in both sides of the brain. Many forms of these seizures are genetically based. There is usually normal neurologic function.
- New classification systems better define specific epilepsies. Some professional groups now suggest that epilepsies be classified in the following five ways:

- Type of seizure (partial or generalized)
- Description of the seizure onset and evolution
- Specific syndromes that are associated with one or more seizure types (however, not all seizures will be part of a syndrome)
- Specific causes of the seizures, if known
- Degree of impairment

- Partial Seizures (also called Focal Seizures)
- These seizures are subcategorized as "simple" or "complex partial."
- ***Simple Partial Seizures:*** A person with a simple partial seizure (sometimes known as Jacksonian epilepsy) does not lose consciousness, but may experience confusion, jerking movements, tingling, or odd mental and emotional events. Such events may include deja vu, mild hallucinations, or extreme responses to smell and taste. After the seizure, the patient usually has temporary weakness in certain muscles.
- ***Complex Partial Seizures:*** Slightly over half of seizures in adults are complex partial type. About 80% of these seizures originate in the temporal lobe, the part of the brain located close to the ear. Disturbances there can result in loss of judgment, involuntary or uncontrolled behavior, or even loss of consciousness. They may lose consciousness briefly and appear to others as motionless with a vacant stare. Emotions can be exaggerated; some sufferers even appear to be drunk. After a few seconds, a patient may begin to perform repetitive movements, such as chewing or smacking of lips. Episodes usually last no more than 2 minutes. They may occur infrequently, or as often as every day. A throbbing headache may follow a complex partial seizure.
- **Generalized seizures** are caused by nerve cell disturbances that occur in more widespread areas of the brain than do partial seizures. Therefore, they have a more serious effect on the patient. They are further subcategorized as tonic-clonic (or grand mal) or absence (petit mal) seizures.
- ***Tonic-Clonic (Grand Mal) Seizures:*** The first stage of a grand mal seizure is called the tonic phase, in which the muscles suddenly contract, causing the patient to fall and lie stiffly for about 10 - 30 seconds. Some people experience a premonition or aura before a grand mal seizure. Most, however, lose consciousness without warning. If the throat or larynx is affected, there may be a high-pitched musical sound (stridor) when the patient inhales. Spasms occur for about 30 seconds to 1 minute. Then the seizure enters the second phase, called the clonic phase. The muscles begin to alternate between relaxation and rigidity. After this phase, the patient may lose bowel or urinary control. The seizure usually lasts

a total of 2 - 3 minutes, after which the patient remains unconscious for a while and then awakens to confusion and extreme fatigue. A severe throbbing headache similar to migraine may also follow the tonic-clonic phases.

- ***Absence (Petit Mal) Seizures****:* Absence or petit mal seizures are brief losses of consciousness that occur for 3 - 30 seconds. Physical movement and loss of attention may stop for only a moment. Such seizures may pass unnoticed by others. Young children may simply appear to be staring or walking distractedly. Petit mal may be confused with simple or complex partial seizures, or even with attention deficit. Attention deficit hyperactivity disorder. In petit mal, however, a person may experience attacks as often as 50 - 100 times a day. About 25% of patients with petit mal develop grand mal seizures. An electroencephalogram (EEG) test that shows a specific brain wave pattern can usually identify these patients.
- Other Seizures
- ***Atonic (Akinetic) Seizures****:*A person who has an atonic (or akinetic) seizure loses muscle tone. Sometimes it may affect only one part of the body so that, for instance, the jaw slackens and the head drops. At other times, the whole body may lose muscle tone, and the person can suddenly fall. A brief atonic episode is known as a drop attack.
- ***Simple Tonic or Clonic Seizure:*** Seizures can also be simply tonic or clonic. In tonic seizures, the muscles contract and consciousness is altered for about 10 seconds, but the seizures do not progress to the clonic or jerking phase. Clonic seizures, which are very rare, occur primarily in young children, who experience spasms of the muscles but not tonic rigidity.
- ***Myoclonic****:* Myoclonic seizures are a series of brief jerky contractions of specific muscle groups, such as the face or trunk.
- **Epileptic Syndromes**:Epilepsy is also grouped according to a set of common characteristics, including:
- Patient age
- Type of seizure or seizures
- Whether a cause is known or not (idiopathic)

A few syndromes and inherited epilepsies are listed as follows.

- ***West Syndrome (Infantile Spasms):*** West syndrome, also called infantile spasms, is a disorder that involves spasms and developmental delay in children within the first year, usually in infants ages 4 - 8 months.
- ***Benign Familial Neonatal Convulsions:*** Benign familial neonatal convulsions (BFNC) are a rare, inherited form of generalized seizures that occur in infancy. BFNC appears to be caused by genetic defects that affect ion channels in nerve cells that carry potassium.
- ***Juvenile Myoclonic Epilepsy (Impulsive Petit Mal):***Juvenile myoclonic epilepsy, also called impulsive petit mal epilepsy, is characterized by generalized seizures, usually tonic-clonic marked by jerky movements (called *myoclonic jerks*), and sometimes absence seizures. This accounts for 7% of epilepsies, and usually occurs in individuals ages 8 - 20.
- ***Adult Myoclonic Epilepsy****:*Some research suggests that adult myoclonic epilepsy may be a previously un-described and distinct syndrome. It involves the development of generalized epilepsy of unknown causes in middle-aged adults.
- ***Lennox-Gastaut Syndrome****:* Lennox-Gastaut syndrome is a severe form of epilepsy in young children that causes multiple seizures and some developmental retardation. It usually involves absence, tonic, and partial seizures.
- ***Myoclonic-Astatic Epilepsy****:* Myoclonic-astatic epilepsy (MAE) is a combination of myoclonic seizures and *astasia* (a decrease or loss of muscular coordination), often resulting in the inability to sit or stand without aid.
- ***Progressive Myoclonic Epilepsy:*** Progressive myoclonic epilepsy is an inherited disorder occurring in children ages 6 - 15. It usually involves tonic-clonic seizures and marked sensitivity to light flashes. Although the disease was previously considered to be progressive throughout life, current therapies have significantly improved its outlook.
- ***Autosomal Dominant Nocturnal Frontal Lobe Epilepsy:*** Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a rare, inherited syndrome that usually occurs during childhood, typically around age 11. However, onset varies widely within families. Seizures can be dystonic (twisting contractions) or tonic

(muscle contractions), or involve thrashing. They are brief, frequent, and occur in clusters during the night. The seizures often subside with age. ADNFLE appears to be caused by an alteration in the brain receptor neuronal nicotinic acetylcholine,

- ***Landau-Kleffner Syndrome:***. Landau-Kleffner syndrome is an epileptic condition that results in the inability to communicate either with speech or by writing (*aphasia*).
- ***Contactin-Associated Protein-Like 2 (CASPR2) Epilepsy*:** CASPR2 is associated with a childhood epilepsy and autism disorder found in closely related relatives in Amish communities.
- **Status Epilepticus**
- Status epilepticus (SE) is a serious, potentially life-threatening, condition that can lead to chronic epilepsy. It occurs in 100,000 - 150,000 people in the U.S. each year, over half of whom are children. Permanent brain damage or death can result if the seizure is not treated effectively.
- The condition is defined as recurrent convulsions that last for more than 20 minutes and are interrupted by only brief periods of partial relief. Although any type of seizure can be sustained or recurrent, the most serious form of status epilepticus is the generalized convulsive or tonic-clonic type. In more than a third of cases, status epilepticus occurs with the first seizure. The trigger is often unknown, but can include the following:
- Failure to take anti-epileptic medications (accounts for about a third of status epilepticus events)
- Abrupt withdrawal of certain anti-epileptic drugs, particularly barbiturates and benzodiazepines
- High fever, poisoning
- Electrolyte imbalances (imbalance in calcium, sodium, and potassium)
- Cardiac arrest, stroke
- Low blood sugar in people with diabetes
- Central nervous system infection

CLASSIFICATON

1.Barbiturate: Phenobarbitone: MOA:GABA facilitatory, GABAmimetic, calcium entry reduction.

2. Deoxybarbitone: Primidone:MOA:deoxybarbiturate,converted by liver to phenobarbitone and phenylethyl malonamide.

3. Hydantoin: Phenytoin:MOA: Prolonging the inactivated state of sodium channel, reduction in calcium influx, inhibition of glutamate, facilititation of GABA.

4. Iminostilbene: Carbamazepine

5. Succinimide: Ethosuximide:MOA:It selectively suppresses T current without affecting other types of Ca^{2+} or Na^{+} currents.It also does not potentiate GABA at therapeutic concentrations.

6. Aliphatic carboxylic acid: Valproic acid

MOA:

i. A phenytoin-like frequency-dependant prolongation of Na^{+} channel inactivation.

ii.weak attenuation of Ca^{2+} mediated 't' current (ethosuximide like).

iii.augmentation of release of inhibitory transmitter GABA by inhibiting its degradation(by GABA-TRANSAMINASE) and increasing its synthesis from glutamic acid.

7. Benzodiazepine:Diazepam,Clonazepam:MOA: chloride conductance(GABA facilitatory action).

8. Phenyltriazine: Lamotrigine:

MOA:prolongation of Na^{+} channel inactivation and suppression of high frequency firing has been demonstrated. In addition ,it may directly block voltage sensitive Na^{+} channels thus stabilizing the presynaptic membrane and preventing release of excitatory neurotransmitters,mainly glutamate and aspartate.

9. Cyclic GABA analogue:**Gabapentin:**MOA:This lipophilic GABA derivative crosses to the brain and enhances GABA release, but does not act as agonist at $GABA_a$ receptor.

2. REVIEW OF LITERATURE

1. **Tomuţă I and Leucuţa SE** reported the development and the in vitro evaluation of extended release multiparticulate dosage forms with carbamazepine, starting from drug crystals of established granulometry as cores and using Eudragit NE aqueous dispersions as coating film polymer in a bottom spray fluid bed coating system. The chosen independent variables, i.e., the quantity of film coating (Eudragit NE) and the % of hydrophilic polymer in film coating that act as pores generating (hydroxypropyl methylcellulose ratio) were optimized. The chosen dependent variables were cumulative percentage values of carbamazepine released after 1, 2, 4, 6, 8 and 12 h and Peppas kinetic release equation parameters (k and n). Based on the experimental design, different carbamazepine formulations were proposed and their release profiles were determined. The dissolution profile of carbamazepine from the coated crystals and tablets prepared with them were similar, and were unchanged after storage for 3 months under controlled conditions.

2. **Cameron F et al.,** Vivus proprietary oral capsule containing phentermine and extended-release (ER) topiramate used for the treatment of obesity. Phentermine is an appetite suppressant, while topiramate is an anti-epileptic medication. The once-daily formulation, known as Qsymia™, is designed to produce weight loss by decreasing appetite and increasing satiety. The product is also in clinical development for sleep apnoea syndrome and type 2 diabetes mellitus.

3. **Sylvain Rheims and Philippe Ryylin** formulated and evaluated once daily lamotrigine extended release for epilepsy management. Once daily XR formulation contains a modified release eroding matix formulation designed to control the dissolution rate of lamotrigine.

4. **Amol Chaudhary** developed once-daily extended release tablet of Lamotrigine, an Anticonvulsant. The tablets were prepared by the wet granulation method. Lamotrigine using hydrophilic matrix material (Methocel K4M & Methocel K100LV) in combination with hydrophobic material (Eudragit L-30D-55) were used, which can release the drug upto 24hrs in predetermined rate. Diluents used were

lactose monohydrate and magnesium stearate as lubricant. The influence of hydrophilic and hydrophobic polymer and granulation technique was studied. The formulated tablets were also characterized by physical and chemical parameters. The granules showed satisfactory flow properties, compressibility, and drug content.

5. **Ye Huang et al.,** The purpose of this study was to investigate the effect of three process variables: distribution of hydroxypropyl methylcellulose (HPMC) within the tablet matrix, amount of water for granulation, and tablet hardness on drug release from the hydrophilic matrix tablets. Tablets were made both by direct compression as well as wet granulation method.

6. **Sandra Furlanetto and Marzia Cirri.,** reported the study of formulation variables influencing the drug release rate from matrix tablets by experimental design. Experimental design was utilized to simultaneously investigate the effect of varying the type of diluent (insoluble Calcium phosphate or water-soluble arabic gum) and the diluent/matrix ratio on the drug release behaviour from both lipophilic (glyceryl behenate, Compritolw) or hydrophilic (hydroxypropylmethylcellulose) matrix tablets. Ketoprofen, theophylline and sodium sulphadiazine were selected as model drugs on the basis of their respectively very low, medium and high water-solubility, in order to evaluate the influence of this parameters.

7. **Meir Bailer et al.,** This review analyses the concept of extended-release (ER) formulations in epilepsy and evaluates ER formulations of carbamazepine, valproic acid and a modified-release (MR) formulation of AED. ER formulations are usually designed to reduce dose frequency and maintain relatively constant or flat plasma drug concentration. It is questionable whether flatplasmaconcentrations of an antiepileptic drug (AED) improve antiepileptic efficacy compared with fluctuating plasma concentrations.

8. **Eman Atef and Albert A. BelmonteEman Atef** developed and characterized a self-emulsifying drug delivery system (SEDDS) of phenytoin, and to compare its relative bioavailability to a commercially available suspension. Four phenytoin SEDDS were prepared and evaluated. Following emulsification, the optimized formula was selected to have the smallest mean particle size and the highest absolute zeta

potential, which should yield the formation of a stable emulsion. In vivo and in vitro tests were run to compare the optimized formula, SEDDS II, to a commercially available Dilantin® suspension. The in vitro dissolution indicated a significant improvement in phenytoin release characteristics. The in vivo study using male rats showed a clear enhancement in phenytoin oral absorption from SEDDS compared to Dilantin® suspension.

9. **Nimmathotta Madhavi N et al.,** The aim of this study is to develop sustained release matrix tablet of phenytoin sodium using eudragit- RL100, eudragit-RS100, HPMC-E15, ethyl cellulose (N-14), Chitosan and HPMC as release controlling factor and to evaluate drug release parameters as per various release kinetic models. The formulated tablets were also characterized by physical and chemical parameters and results were found in acceptable limits. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Based on "n" value (0.168) the drug release followed Fickian diffusion. Also the drug release mechanism was best explained in Higuchi order by using this polymer.

10. **Rompicharla Bhargavi et al.,** formulated, developed and evaluated gabapentin matrix tablets**.** Gabapentin is an anti epileptic drug used for the treatment of epileptic seizures and in treatment of post therapeutic neuralgia. In this study controlled released Gabapentin matrix tablets were prepared by using different matrix forming polymers which include hydrophilic polymers like HPMC K15M, HPMC K100M, Xanthan gum and hydrophobic polymer like Ethylcellulose in various ratios to retard the release of drug upto 12hrs. The formulations containing the combination of hydrophilic and hydrophobic polymer combinations (HPMC K100M with Ethycellulose) and the formulations prepared with the combination of two hydrophilic polymers of synthetic and natural origin (HPMC K100M with Xanthan Gum) exhibited maximum drug release(99%) upto12hrs during *in vitro* dissolution studies with optimum swelling characteristics.

11. **Wael Ali et al.,** formulated and evaluated Carbamazepine 200 mg Controlled Release Tablets Using Different HPMC Grades. Possible interaction between carbamazepine and different HPMC grades was done using DSC thermal analysis. Seven preparations of carbamazepine 200 mg controlled release tablets were

prepared by wet granulation method and one preparation was prepared by direct compression method where different HPMC grades with different ratios were used. Concerning uniformity of weight, hardness and assay; all tablets conformed to pharmacoepial limits. Dissolution of the prepared tablets was done using basket method for 24 hours and paddle method for 4 hours. Drug release kinetics was under zero order.

12. **Alfred Fahr et al.,** reported physicochemical characterization of solid dispersions of three antiepileptic drugs prepared by solvent evaporation method. We have investigated the solid dispersion and dissolution profiles of three antiepileptic drugs (carbamazepine, rufinamide, and an AED) with different aqueous solubilities, prepared by the solvent evaporation method. Solid dispersions of the three drugs in hydroxy-propylmethylcellulose (HPMC), with drug:polymer ratios of 1:4, were prepared and characterized by differential scanning calorimetry (DSC), Fourier transformation infrared (FTIR) spectroscopy, X-ray diffraction (XRD) and scanning electron microscopy. The release mechanism was also investigated and the kinetic order of the solid dispersions was evaluated. Thus, solid dispersions of these drugs had an improved dissolution profile.

13. **R. Valarmathi et al.,** made a review on Lacosamide (LCM) and its analytical methods. Lacosamide, a new antiepileptic drug approved by US-FDA for the treatment of partial onset seizure. Lacosamide has less severe side effects and less drug interactions with other drugs. There are several analytical methods including UV, HPLC, HPTLC have been reported for determination of lacosamide in its pharmaceutical dosage forms. Lacosamide in human and rat plasma is determined using LC-MS. Stability indicating HPLC have also been reported for Lacosamide.

14. **Swati Dubey et al.,** Simultaneous determination of three traditional and two novel Antiepileptic Drugs using Micellar Liquid Chromatography. This paper discussed about the determination of five antiepileptic drugs (carbamazipine, clobazam, lamotigine, phenytoin and topiramate) using C18 column (5µm, 250×4.6mm) hybrid mobile phases containing sodium dodecyl sulfate (SDS) as surfactant and pentanol as modifier. Detection was performed with a diode array detector at 230nm.

15. **Harshal Pawar et al.,** A simple, precise and reproducible reverse phase, isocratic high performance liquid chromatographic (HPLC) method was developed and validated for the quantitative determination of Valproic Acid in the dissolution study of Pharmacosomes. The quantification was carried out using a Zorbax Eclipse XBD-C18 (4.6 × 150mm, 5 µm) column, with a mobile phase consisting of Acetonitrile: Citric acid buffer (50:50, v/v) (pH 3) at a flow rate of 1.5 ml/min and UV detection at 210 nm. The method was validated for specificity, method precision, linearity, recovery, robustness, ruggedness and solution stability. The proposed method was successfully applied for determination of the Valproic Acid in dissolution study of Pharmacosomes

16. **Emilio Perucca** demonstrated Extended-Release Formulations of Antiepileptic Drugs: Rationale and Comparative Value Extended-release products are designed to prolong the absorption of drugs with short half-lives, thereby allowing longer dosing intervals while minimizing fluctuations in serum drug levels. The relationship between serum drug concentration and clinical effects of antiepileptic drugs (AEDs) can be complex and reducing fluctuations in serum drug levels is not equally advantageous for all AEDs. Extended-release formulations have been shown to be particularly valuable for carbamazepine.

17. **Imran Ali et al.,** compared the pharmacokinetics (PK) of lamotrigine (LTG) when converting from twice-daily immediate-release (LTG-IR) to once-daily extended-release (LTG-XR) in subjects with epilepsy.

18. **J. Emami et al.,** A simple HPLC method was developed and validated for quantitation of lamotrigine and its related substances which may coexist in solid pharmaceutical dosage forms. The HPLC separation was achieved on a C18 µ column (250 mm × 4.6 mm) using a mobile phase of acetonitrile–monobasic potassium phosphate solution (35:65, v/v) containing orthophosphoric acid to adjust pH to 3.5 at a flow rate of 1.5 ml/min. The UV detector was operated at 210 nm, and column temperature was adjusted at 40 °C. The method was validated for specificity, linearity, precision, accuracy, robustness and limit of quantitation.

19. **Abhay Gupta et al.,** studied the Development and application of a validated HPLC method for the determination of gabapentin and its major degradation impurity in drug products.

20. **Md Sajid Ali et al.** developed sustained release matrix tablets of phenytoin sodium an antiepileptic drug. The tablets were fabricated by the wet granulation method using water as granulating agent along with matrix materials like guar gum, sodium alginate, tragacanth and xanthan gum with varying percentage. The granules were evaluated for angle of repose, bulk density, compressibility index, total porosity, and drug content. The tablets were subjected to weight variation test, drug content, hardness, friability, and in vitro release studies. The swelling behaviour of matrix was also investigated. The most successful exhibited satisfactory drug release and extended the release up to 12 hours. The mechanism of drug release from all the formulations was diffusion coupled with erosion.

3. AIM & OBJECTIVE OF WORK

AIM:

The aim of the work is to design and develop Extended Release (ER) tablets of an anticonvulsant drug and to carry out the in- vitro release study of the drug.

OBJECTIVES:

- To carry out preformulation and physicochemical characterization of drug and excipients.
- To formulate extended release tablets of anticonvulsant drug.
- To optimize the ER formulations based on pre and post compression characterization.
- To carry out stability studies as per ICH guidelines.

4. PLAN OF WORK

- Fourier Transform Infrared Spectroscopy (FTIR): To study the possible chemical interaction between the Excipient and drug.
- Preparation of extended release tablets of anti-convulsant drug containing matrix releasing polymer by Wet Granulation method.
- Evaluation of blend
    - Angle of repose
    - Bulk density and tapped density
    - Compressibility index
    - Hausner's Ratio
- Evaluation of tablets
    - Weight variation
    - Hardness
    - Friability
    - Thickness
    - Content Uniformity
    - Kinetic modeling
    - Evaluation of in vitro release characteristics using USP dissolution apparatus 2 (paddle).
- Intermediate and accelerated stability studies of optimized formulation as per ICH guidelines to be performed.

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5. DRUG PROFILE

Category: Anti-epileptic drug

Description:

Yellow crystalline powder

Solubility:

Soluble in acetic acid, sparingly soluble in chloroform, practically insoluble in water

Mechanism of action:

The pharmacologic activity is primarily through the active metabolite of the drug, but the exact mechanism is unknown. It may block voltage-sensitive sodium channels, resulting in stabilization of hyperexcited neural membranes, inhibition of repetitive neuronal firing, and diminution of propagation of synaptic impulses.

Pharmacodynamics:

Changing the molecular structure of the drug helps in reducing the impact on the liver and prevents the serious forms of anemia occasionally associated with the drug. Aside from this reduction in side effects, it is thought to have the same mechanism as carbamazepine - sodium channel inhibition - and is generally used to treat the same conditions.

Pharmacokinetics

Absorption

Completely absorbed and extensively metabolized to active metabolite. Steady-state concentrations of active metabolite of drug are reached in 2 to 3 days when given twice daily. For tablet form, T max is 4.5 h. For oral suspension form, T max is 6 h. Food had no effect on the rate and extent of absorption.

Distribution

The apparent volume of distribution (Vd) for active metabolite is 49 L. Approximately 40% of active metabolite is protein bound, predominantly to albumin.

Metabolism

Rapidly reduced by cytosolic enzymes in the liver to active metabolite, which is primarily responsible for the pharmacologic effect. Active metabolite is metabolized further by conjugation with glucuronic acid. 4% is oxidized to inactive 10,11-dihydroxy metabolite (DHD).

Elimination

Less than 1% eliminated unchanged through the kidneys. 80% excreted as glucuronides of active metabolite (49%) or as unchanged (27%); inactive DHD accounts for 3% and conjugates of active metabolite account for 13%.

Adverse reactions:

The most commonly observed adverse reactions seen in association with drug were dizziness, somnolence, headache, balance disorder, tremor, vomiting, diplopia, asthenia, and fatigueness.

Half Life:

The half-life of the parent is about 2 hours, while the half-life of active metabolite about 9 hours, so that active metabolite is responsible for most anti-epileptic activity.

6. EXCIPIENTS PROFILE

A. HYDROXY PROPYL METHYL CELLULOSE

Synonyms:

Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose;MHPC

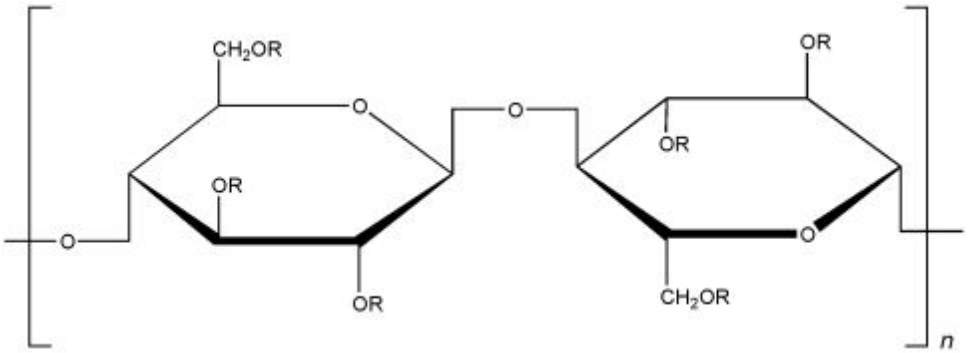
Official Status: BP: Hypromellose

JP: Hypromellose

PhEur: Hypromellose

USP: Hypromellose

STRUCTURAL FORMULA:



where R is H, CH_3, or $CH_3CH(OH)CH_2$

Functional Category:

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent;tablet binder; thickening agent; viscosity-increasing agent.

Description:

Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder. HPMC K 15M can successfully be used in mortars and plasters which are manually applied. The product imparts good workability to mortars and plasters and enhances water retention. HPMC 15CPS and HPMC K 4M cellulose derivatives also been used as in these formulation.

Solubility: Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of Hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol.

Grades:

Higher viscosity grades leading to greater diffusional resistance to water. This directly reduces the diffusion of drug out of the matrix and indirectly affects the state of hydration within the gel, thus affecting that component of drug release due to erosion of the dosage form. **Methocel K 4M (4000 Cps), K 15M (15000 Cps) and K 100M (100000 Cps)** were similar despite differences in viscosities. Methocel K 100M>Methocel K 15M>Methocel K 4M based on viscosities.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritating to the eyes, so eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Storage:

Hydroxy Propyl Methyl Cellulose powder should be stored in a well-closed container, in a cool, dry place.

B. LACTOSE MONOHYDRATE

Synonyms:

CapsuLac; GranuLac; Lactochem; lactosum monohydricum; Monohydrate; Pharmatose;PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose.

Official Status: BP: Lactose
PhEur: Lactose Monohydrate
JP: Lactose Hydrate
USP-NF: Lactose Monohydrate

Structural Formula: $C_{12}H_{22}O_{11}.H_2O$

Functional Category:

Dry powder inhaler carrier; lyophilization aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

Description:

In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying conditions, i.e. lactose monohydrate, b-lactose anhydrous, and lactose anhydrous. The stable crystalline forms of lactose are a-lactose monohydrate, b-lactose anhydrous, and stable a-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odourless and slightly sweet-tasting; a-lactose is approximately 20% as sweet as sucrose, while b-lactose is 40% as sweet.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive generation of dust, or inhalation of dust, should be avoided.

C. POVIDONE (PVP K-30)

Synonyms:

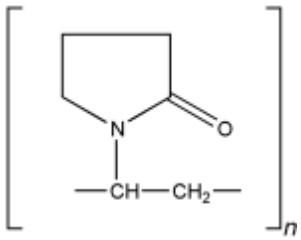
E1201; Kollidon; Plasdone; poly[1-(2-oxo-1-pyrrolidinyl)ethylene]; polyvidone; polyvinylpyrrolidone; povidonum; Povipharm; PVP; 1- vinyl-2-pyrrolidinone polymer.

Official Status: BP: Povidone
JP: Povidone
PhEur: Povidone
USP: Povidone

Functional Category:

Disintegrant; dissolution enhancer; suspending agent; tablet binder.

Structural Formula:



Povidone occurs as a fine, white to creamy-white coloured, odourless or almost odourless, hygroscopic powder. Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol, and water, practically insoluble in ether, hydrocarbons, and

mineral oil. In water, the concentration of a solution is limited only by the viscosity of the resulting solution, which is a function of the K30 value.

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection, gloves, and a dust mask are recommended.

Storage:

Povidone may be stored under ordinary conditions without undergoing decomposition or degradation. However, since the powder is hygroscopic, it should be stored in an airtight container in a cool, dry place.

D.COLLOIDAL SILICON DIOXIDE

Synonyms:

Aerosil; Cab‐O‐Sil; colloidal silica; fumed silica; light anhydrous silicic acid; silicic anhydride; silicon dioxide fumed.

Official Status: BP: Colloidal Anhydrous Silica
JP: Light Anhydrous Silicic Acid
PhEur: Silica, Colloidal Anhydrous
USP-NF: Colloidal Silicon Dioxide

Structural Formula: SiO_2

Functional Category:

Adsorbent; anti caking agent; emulsion stabilizer; glidant; Suspending agent; tablet disintegrant; thermal stabilizer; viscosity‐increasing agent.

Description:

Colloidal silicon dioxide is sub microscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish white - coloured, odourless, tasteless, non gritty amorphous powder.

Solubility:

Practically insoluble in organic solvents, water, and acids, except hydrofluoric acid; soluble in hot solutions of alkali hydroxide. Forms a colloidal dispersion with water.

Handling Precautions:

Eye protection and gloves are recommended. Precautions should be taken to avoid inhalation of colloidal silicon dioxide. In the absence of suitable containment facilities, a dust mask should be worn when handling small quantities of material. For larger quantities, a dust respirator is recommended.

E.MAGNESIUM STEARATE

Synonyms:

Magnesium octadecanoate, octadecanoic acid, magnesium salt, stearic acid, magnesium salt.

Structural Formula: $[CH_3 (CH_2)_{16}COO]_2Mg$

Official Status: BP: Magnesium Stearate
JP: Magnesium Stearate
PhEur: Magnesium Stearate
USP-NF: Magnesium Stearate

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Functional Category:

Tablet and capsule lubricant

Solubility:

Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%)

Handling Precautions:

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking. Magnesium stearate should be handled in a well‐ventilated environment; a respirator is recommended.

Storage:

Magnesium stearate is stable and should be stored in a well closed container in a cool, dry place.

F.CARBOXY METHYL CELLULOSE SODIUM

Nonproprietary Names: BP: Carmellose sodium
JP: Carmellose
PhEur: Carmellosum natricum
USP: Carboxymethylcellulose sodium

Synonyms:

Akucell; *Aquasorb*; *Blanose*; cellulose gum; CMC sodium; E466; *Finnfix*; *Nymcel*; SCMC;sodium carboxymethylcellulose; sodium cellulose glycolate; sodium CMC; *Tylose CB*.

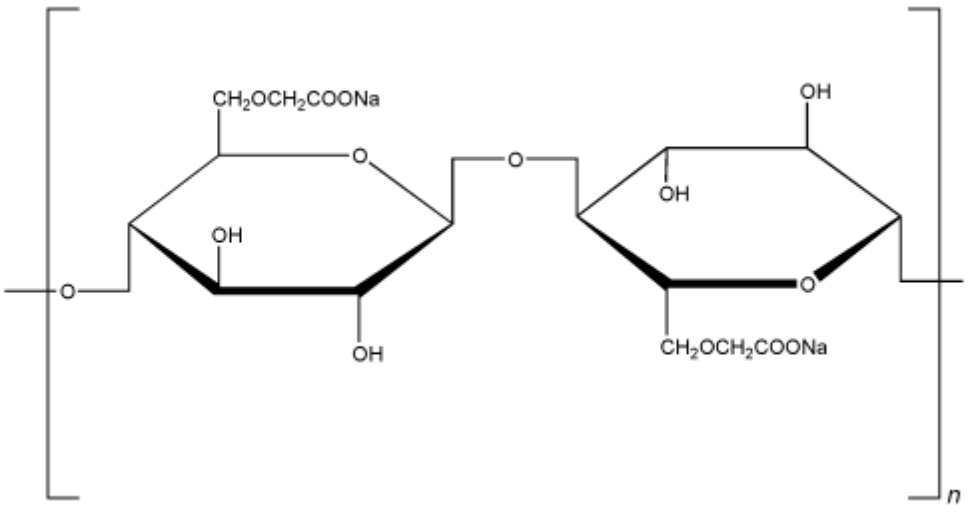
Functional Category:

Coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tabletbinder; viscosity-increasing agent; water-absorbing agent.

Description:

Carboxymethylcellulose sodium occurs as a white to almost white, odorless, granular Powder.

Structural Formula:



Stability and Storage Conditions:

Carboxymethylcellulose sodium is a stable, though hygroscopic material.Aqueous solutions are stable at pH 2–10; precipitation can occur below pH 2, and solutionviscosity decreases rapidly above pH 10. Generally, solutions exhibit maximum viscosity and stability at pH 7–9.

The bulk material should be stored in a well-closed container in a cool, dry place.

7. MATERIALS AND METHODOLOGY

Sr. no.	Materials used	Grade	Manufacturer
1	API	IP	Sun Pharma
2	HYPROMELLOSE K4M	USP/NF	Colorcon
3	HYPROMELLOSE K15M	USP/NF	Colorcon
4	CARBOXY METHYL CELLULOSE SODIUM	IP	FMC
5	LACTOSE MONOHYDRATE	USP	DMV Fonterra
6	POVIDONE	USP	BASF Ltd
7	COLLOIDAL SILICON DIOXIDE	USP	Evonik
8	MAGNESIUM STEARATE	USP	Amishi drugs and chemicals
9	INSTACOAT YELLOW	USP	Colorcon

Table 1: **List of chemicals used with grade and supplier**

S.NO	EXCIPIENTS	FUNCTIONAL CATEGORY
1	Drug	Active Ingredient
2	HPMC K15M/K4M	Matrix forming Polymer
3	Lactose monohydrate	Diluent
4	Povidone	Binder
5	Colloidal silicon dioxide	Glidant
6	Magnesium Stearate	Lubricant
7	Purified Water	Solvent for granulation

Table 2: List of ingredients with their functional category

Sr. no	Instrument	Manufacturer
1	Analytical Balance	Sartorius BT224S
2	Top Loading Balance	Sartorius CPA8201
3	Tapped Density Tester	Electrolab ETD-1020
4	Vibrator Sifter	Gansons engg.pvt.ltd GMP-LAB Sr no. 236
5	Octagonal blender	Ganson engg.pvt.ltd. GMP ,STD
6	TabletCompression machine 16 station	CADMACH, Ahemdhabad.
7	Digital Vernier caliper	Mituyutoyo
8	IRMoisture analyser/Balance (LOD)	Sartorius MA150
9	Tablet hardness tester 8M	Dr.Schleuniger pharmatron 8M
10	Friabilator USP	Electrolab EF-2

11	High Performance Liquid Chromatography	SHIMADZU LC 2010 C HT
12	Dissolution Test apparatus	LABINDIA DISSO 8000
13	Fourier Transform Infrared Spectrophotometer (FT-IR)	SHIMADZU,IR PRESTIGE-21
14	Ultravoilet-visible Spectrophotometer	SHIMADZU UV-1700 Pharmaspec.
15	Rapid Mixer Granulator	Sainath Boilers

Table 3: List of equipments used

DRUG EXCIPIENT COMPATIBILITY STUDY

API and excipients were thoroughly mixed in predetermined ratio as per in the given table and passed through the sieve No.40. The blend was filled in 10 ml glass vials and closed with gray rubber stoppers and sealed with aluminum seal and charged in to stress condition at 25ºC/60%RH. Similarly API was also kept at above conditions as like the samples. The samples were observed for any physical change in 15th and 30th days.

SERIAL NO.	COMPOSITION DETAILS	RATIO
1	Only API	1
2	API+HPMCK4M Premium	1:1
3	API+HPMCK15M premium	1:0.5
4	API+CMC sodium	1:1
5	API+povidone	1:0.5
6	API+colloidal silicon dioxide	1:0.1
7	API+magnesium stearate	1:0.25
8	API+lactose monohydrate	1:5

Table 4: Composition of API with different excipients used for compatibility study

FORMULATION DESIGN

INGREDIENTS	QUANTITY USED IN THE FORMULATION (mg per tablet)					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
API	150	150	150	150	150	150
HPMCK15M	-	-		50	35	35
HPMCK4M	30	35	37.5		-	-
CMC Sodium	15	10	10	-	-	-
Lactose monohydrate	81.048	81.049	78.545	76.049	91.5	91.5
Povidone(PVPK30)	5	5	5	5	5	5
Colloidal Silicon dioxide	1	1	1	1	1	1
HPMCK15M HPMCK4M	- 15	- 15	- 15	15 -	15 -	15 -
Magnesium stearate	2.5	2.5	2.5	2.5	2.5	2.5
Purified Water	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight	300	300	300	300	300	300

Table 5: Formula for extended release tablets

MANUFACTURING PROCEDURE

STEP I: DISPENSING OF MATERIALS

All the raw materials are dispensed, packed in an individual clean poly bags and labeled.

STEP II: SIFTING

API, HPMC(K4orK15M) and lactose monohydrate sifted through #40 mesh.

STEP III: PREPARATION OF BINDER SOLUTION

Povidone was diluted in sufficient quantity of water.

STEP IV: DRY MIXING:

Materials were loaded in RMG and are mixed for about 15 minutes at slow speed.

STEP V: GRANULATION

Binder solution is added to the dry mix at slow speed. After the addition of the binder, it is mixed for about three minutes at fast speed to form granules.

STEP VI: DRYING

Load blend in rapid dryer at a temperature of 60^0 and air flow about 40. Drying is continued until loss on drying reaches NMT 2%.

STEP VII: SIZING

Milled in a multimill using 1.5mm screen. Blend was sifted through 20#mesh.

STEP VIII: PRE LUBRICATION

Aerosil, HPMC(K4orK15M) was sifted through 40#mesh and kept aside. Load this in octagonal blender along with the blend.

STEP IX: LUBRICATION

Magnesium stearate was sifted through 60#mesh and added to the above step and mixed for 2 minutes in blender.

STEP X: COMPRESSION

Compression was carried out in 8stn. Physical parameters like Weight variation, Hardness, Thickness, are monitored to meet the predefined specifications and noted.

Punch dimensions (diameter)	9.5mm
Punch shape	Standard concave plain

STEP XI: COATING

25grams of instacoat yellow in 250ml of water kept under mechanical stirring for about 20minutes.Coating is done with temperature of 70^{o}c with pump rpm of 0-1. Coating is done under F4-F6 trials.

PRECOMPRESSION PARAMETERS

Determination of bulk density and tapped density

A quantity of 5g of the powder (W) from each formula was introduced into a 25 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5cm at 2 sec intervals. The tapping was continued until to further change in volume was noted. The bulk density and tapped density were calculated using the following formulas.

Bulk density=W/V_0

Tapped density=W/V_t

Where, W=weight of the powder,

V_0 =initial volume,

V_t = tapped volume

Hausner's ratio

Hausner's ratio provides an indication of the flow properties of the powder, which could result from vibration of the feed hopper. A lower value of indicates better flow and vice versa.

Hausner's ratio = Tapped density /Bulk density

HAUSNER RATIO	TYPE OF FLOW
Less than 1.25	Good Flow (20% Carr's index)
1.25 – 1.5	Moderate (33% Carr's index) (adding glidant normally improves flow)
Greater than 1.5	Poor Flow (Glidant has marginal effect)

Table 6: Specifications of Hausner's ratio

Carr's Compressibility Index

Compressibility is the ability of powder to decrease in volume under pressure. Compressibility is a measure that is obtained from density determinations. It is also one of the simple methods to evaluate flow property of powder by comparing the bulk density and tapped density. High density powders tend to possess free flowing properties. A useful empirical guide is given by the Carr's index or compressibility index calculated from bulk density and tapped density.

Carr's index= (Tapped density- Bulk density/ Tapped density) ×100

% COMPRESSIBILITY	FLOW DESCRIPTION
<10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Extremely poor

Table 7: Relationship between %compressibility and flow description

ANGLE OF REPOSE

The frictional force in a loose powder can be measured by the angle of repose. Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by Fixed Funnel Method and is the measure of the flow ability of powder/granules. A funnel with 10 mm inner diameter of stem was fixed at a height of 2 cm. over the platform. About 10 gm of sample was slowly passed along the wall of the funnel till the tip of the pile formed and touches the steam of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured.

Angle of repose was calculated from the average radius using the following formula.

$$\theta = \tan^{-1} (h/r) = \tan^{-1} (\text{height of pile}/0.5\text{base})$$

Where,

θ = Angle of repose

h = Height of the pile

r = Average radius of the powder cone

ANGLE OF REPOSE	TYPE OF FLOW
< 25	Excellent
25 – 30	Good
30 – 40	Passable
> 40	Very Poor

Table 8: Specifications of angle of repose

POST COMPRESSION EVALUATION PARAMETERS FOR FORMULATED TABLETS

General Appearance

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, color, presence or absence of odour, taste etc.

Size and Shape

It can be dimensionally described & controlled. The thickness of a tablet is only a variable. Tablets thickness can be measured by Digital Vernier calipers. Tablet thickness should be controlled within a 7.5% variation of standard value.

Hardness

Tablet requires a certain amount of strength or hardness and resistance to friability to withstand mechanical shake of handling in manufacture, packing and shipping. Hardness generally measures the tablets crushing strength. The hardness of all the formulations was checked using

Dr.Schleuniger pharmatron 8M hardness tester. The average hardness of 10 tablets of all the batches were measured and reported.

Friability

Friability of a tablet can determine in laboratory by Electro lab EF2 Friabilitor. This consist of a plastic chamber that revolves at 25 rpm, dropping the tablets of weight not less than 6.5 g, through a distance of six inches in the Friabilator, which is then operate for 100 revolutions. The tablets are reweighed. Compressed tablets that less than 0.1 to 0.5% of the tablet weight are considered acceptable. The percentage friability was measured using the formula

$$\%F = \{1-(W/W_0)\} \times 100$$

Where, %F =friability in percentage

W_0 = Initial weight of tablet

W = Weight of tablets after revolution.

Weight variation

Take 20 tablets and weigh individually. Calculate average weight and compare the individual tablet weight to the average. The tablet pass the B.P. test if no more than 2 tablets are outside the percentage limit and if no tablets differs by more than 2 times the percentage limit.

Average weight of tablet (mg)	Maximum% difference allowed
80 mg or less	10
80 mg to 250 mg	7.5
More than 250 mg	5

Table 9: Weight variation limit as per BP

UNIFORMITY OF DRUG CONTENT: The drug content was performed to check the dose uniformity in the formulation. Randomly ten tablets were weighed and powdered. As following of assay procedure after suitable dilutions, the drug content was determined by HPLC at 215nm.

ASSAY

Particulars	API
Column	C18 250 mm × 4.6 mm 5µ(Thermohypersil BDS)
Flow rate	2.0 ml/min.
Detector	UV/PDA detector
Wavelength	215nm
Injection volume	20µl
Column temperature	25°C
Run time	10 minutes
Elution	Isocratic
Buffer	Dissolve 6.8g of potassium dihydrogen phosphate in 1000 ml milli-Q water,dissolve and mix well and filter through 0.45µ nylon membrane disc filter.
Mobile phase	Mix buffer, acetonitrile, methanol and triethylamine in the ratio of 660:140:200:1(v/v) and adjust the pH to 6.0 with dilute orthophosphoric acid sonicate to degas.
Diluent	Use mobile phase
Standard	Weigh accurately about 25.0mg of API working standard into 50ml volumetric flask, add about 30ml of methanol, sonicate for 15minutes to dissolve with intermittent shaking and dilute to 50ml with methanol, and mix well. Pipette and dilute 5ml of resulting solution into 25ml volumetric flask, and dilute to 25ml with diluent and mix well. Centrifuge a portion of this solution at 3000rpm for 10minutes and use this as standard solution.
Sample	Weigh and powder 20 tablets. Accurately weigh and transfer tablet powder equivalent to 50mg of API into a 100ml volumetric flask, add about 70ml of methanol, sonicate for about 30 minutes to dissolve the contents and dilute to 100ml with methanol and mix well. Centrifuge a portion of this solution at 3000rpm for 10minutes. Pipette and dilute 5ml of resulting into 25ml volumetric flask, and dilute to 25ml with diluents.

Table 10: Chromatographic conditions for assay

Procedure for API:

Equilibrate the column with the mobile phase until a baseline is obtained. Inject the sample and standard solutions. Record the chromatogram and measure the peak area response of both standard and sample preparations of the API.

Calculation for percentage of API:

$$\% \text{ assay of API} = \frac{AT}{AS} \times \frac{WS}{50} \times \frac{5}{25} \times \frac{100}{WT} \times \frac{P}{100} \times \frac{25}{5} \times \frac{AW}{LC} \times \frac{P}{100} \times 100$$

Where,

AS = area obtained in test sample.

AT and = average area of standard sample.

WS = weight of working test sample taken in milligrams.

LC = Labeled amount of API in mg/ tablet.

P = % potency of the API working standard on as in basis.

AW = Average weight of tablet

WT=weight of powdered tablet taken in mg for sample preparation.

***In-Vitro* DISSOLUTION STUDY**

Particulars	API
Column	C18 250 mm × 4.6 mm 5µ(Thermo Hypersil BDS is suitable)
Flow rate	2.0 ml/min.
Detector	UV/PDA detector
Wavelength	215 nm
Injection volume	20µl
Column temperature	25°C
Run time	10 minutes
Elution	Isocratic
Mobile phase	660:140:200:1 ratio of buffer, acetonitrile,methanol and triethylamine

Diluent	Mobile phase

Table 11: Chromatographic Conditions for the dissolution study of API

Dissolution parameters	API
Medium	1% w/v Solution of SLS
Apparatus	USP apparatus Type II
Volume	900 ml
Agitation	50 rpm
Measuring time	30minutes
Temperature	37°C±0.5°C
Volume withdrawn	10ml

Table 12: Dissolution conditions for API

STANDARD PREPARATION FOR API

Weigh accurately about 25.0mg of API working standard into 50ml volumetric flask, add about 30ml of methanol, sonicate for 15minutes to dissolve with intermittent shaking and dilute to 50ml with methanol, and mix well. Pipette and dilute 5ml of resulting solution into 25ml volumetric flask, and dilute to 25ml with diluent and mix well. Centrifuge a portion of this solution at 3000rpm for 10minutes and use this as standard solution.

SAMPLE PREPARATION FOR API

Weigh and powder 20 tablets. Accurately weigh and transfer tablet powder equivalent to 50mg of API into a 100ml volumetric flask, add about 70ml of methanol, sonicate for about 30 minutes to dissolve the contents and dilute to 100ml with methanol and mix well. Centrifuge a portion of this solution at 3000rpm for 10minutes. Pipette and dilute 5ml of resulting into 25ml volumetric flask, and dilute to 25ml with diluents.

PROCEDURE

Equillibrate the column with mobile phase for sufficient time until stable baseline is obtained. Inject blank, standard and sample preparation into the chromatographic system. Record the

chromatogram and measure the peak area response for API. Inject the standard solution as bracketing after every 6 injections of sample solution.

SYSTEM SUITABILITY PARAMETERS

1. In the chromatograms obtained with the standard preparation, %RSD for 5 replicate injections of API peak shall be not more than 2.0.
2. In the chromatograms obtained with the standard preparation, USP theoretical plates obtained for API peak shall be not less than 2000.
3. In the chromatograms obtained with the standard preparation, USP tiling factor obtained for API peak shall be not more than 2.0.

Procedure:

Equilibrate the system with the mobile phase for sufficient time until stable baseline is observed. Inject dissolution medium as blank, standard preparation, sample preparation. Inject standard preparation as bracketing after six injections of sample preparation.

Drug	Specification
API	After 2nd hour, not more than 30% After 6th hour 30% to 60% 12th hour Not less than 85%

Table 13: Specifications for Drug release

DATA ANALYSIS

The data obtained from the dissolution study were subjected for analysis to know the release pattern of the drug from the dosage form.

To analyze the mechanism of release and release rate kinetics of the dosage form, the data obtained were fitted into Zero order, First order kinetic, Higuchi model kinetic and Korsmeyer-Peppas model. Based on the r-value, the best-fit model was selected.

Zero Order Kinetics:

It describes the system in which the drug release rate in independent of its concentration.

$$Q_t = Q_o + K_o t$$

Where,

Q_t = amount of drug dissolved in time t.

Q_o = initial amount of the drug in the solution and

K_o = zero order release constant.

If the zero order drug release kinetic is obeyed, then a plot of % drug release versus time will give a straight line with a slope of K_o and intercept at zero.

FIRST ORDER KINETICS:

It describes the release from the systems in which the release rate is concentration dependent.

$$\log Q_t = \log Q_o + k_t / 2.303$$

Where,

Q_t = amount of drug released in time t.

Q_o = initial amount of drug in the solution.

K_t = is the first order release constant.

If the first order drug release kinetic is obeyed, then a plot of log % drug remaining to be released versus time will be straight line with a slope of k_t / 2.303 and an intercept at t=0 of log Qo.

HIGUCHI MODEL:

It describes the fraction of drug release from a matrix is proportional to square root of time.

$Mt / M\infty = kHt^{1/2}$

Where,

Mt and M∞ = cumulative amount of drug release at time t and infinite time.

kH = Higuchi dissolution constant reflection formulation characteristics.

'F' is the amount of drug release, 'K' is the release rate constant, and't' is the release time.

If the Higuchi Model of drug release is obeyed, then a plot of cumulative % drug release versus $t^{1/2}$ will be straight line with slope of kH.

KORSMEYER - PEPPAS MODEL:

The power law describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation,

$\log [Mt / M\infty] = \log k + n \log t$

Where,

Mt and M∞ = cumulative amounts of drug release at time t and infinite time.

k = constant incorporating structure and geometrical characteristics of CR device.

n = diffusion release exponent indicative of mechanism of drug release for drug dissolution.

A plot of log [Mt / M∞] (log % drug release) versus log time(log t) will be linear with slope of n and intercept gives the value of log k. Antilog of log k gives the value of k.

STABILITY STUDIES

Introduction:

The ICH Q1A guideline defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the EC, Japan, and the United States. It does not seek necessarily to cover the testing for registration in or export to other areas of the world.

Method:

Stability studies were carried out at 30°C ± 2°C/65% RH ± 5% RH for 12 months and at 40°C ± 2°C/75% RH ± 5% RH for 6 months for the selected formulation.

The stability studies were done for formulation 5 (F5). These formulations were selected depending upon the *in-vitro* drug release study of ER form. The formulation was charged for stability for different stability studies.

Formulation	**Stability condition**	**Testing frequency**	**Tests**
Selected Formulation	30°C ± 2°C/65% RH ± 5% RH	3rd month 6thmonth 9th month 12th month	Appearance, Physical Parameters, Assay, Uniformity of weights, In vitro drug release.
	40°C ± 2°C/75% RH ± 5% RH	1st month 2ndmonth 3rd month 6thmonth	

Table 14: Stability testing Protocol

8. RESULTS AND DISCUSSION

Drug Solubility Studies:

Quantity of API- 1	Quantity of solvents	Inference
100 mg	100 ml of Triethylamine	Soluble
100 mg	100 ml of methanol	Sparingly soluble
100 mg	100ml of chloroform	Sparingly soluble
100 mg	100 ml of acetonitrile	Soluble
100 mg	100 ml of acetic acid	Soluble

Table 15: Drug solubility studies

Evaluation of Active pharmaceutical ingredients:

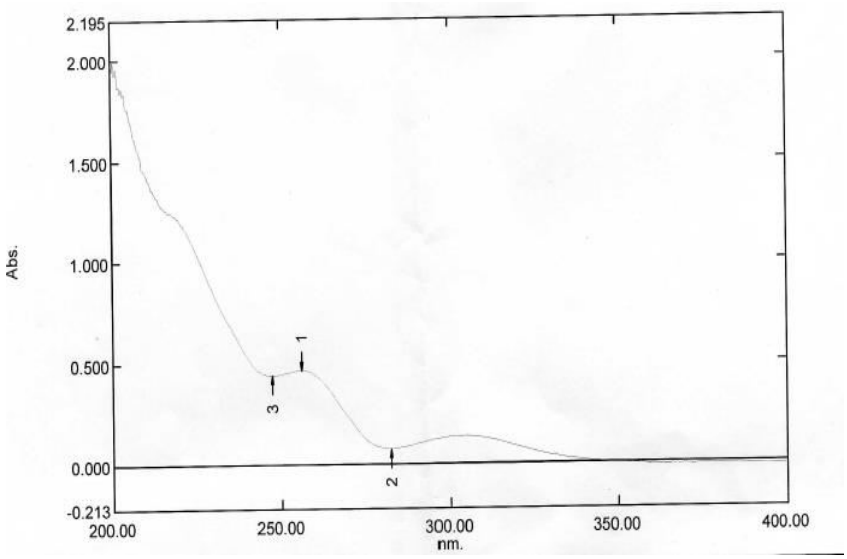
Physical parameters like Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's index and Solubility of the API was determined and were given here in the table below.

Parameters	API
Solubility	Soluble in acetic acid, sparingly soluble in chloroform and practically insoluble in water.
Angle of repose	25.50
Bulk density	0.445gm/cm^3
Tapped density	0.666 gm/cm^3
Carr's index	21.80
Hausner's ratio	1.329
Loss on drying	1.45%
Assay	99.82%

Table 16: Results for Pre-formulation analysis of API

The solubility, Loss on drying, Assay of the drugs are found to be within the specifications. From the Compressibility index, Angle of repose values of API, it can be concluded that API have poor flow and this can be improved by granulation.

DETERMINATION OF LAMBDA MAX



No.	P/V	Wavelength	Abs.	Description
1	⊕	256.20	0.466	

Fig6: lambda max curve

FTIR STUDY

The samples that were charged in 30^0C/65%RH and 40°C/75% RH stability chambers were analysed by IR spectroscopy after 30 days. The graphs of the samples were given below.

Fig7: FTIR Study of API+HPMC K4M PREMIUM

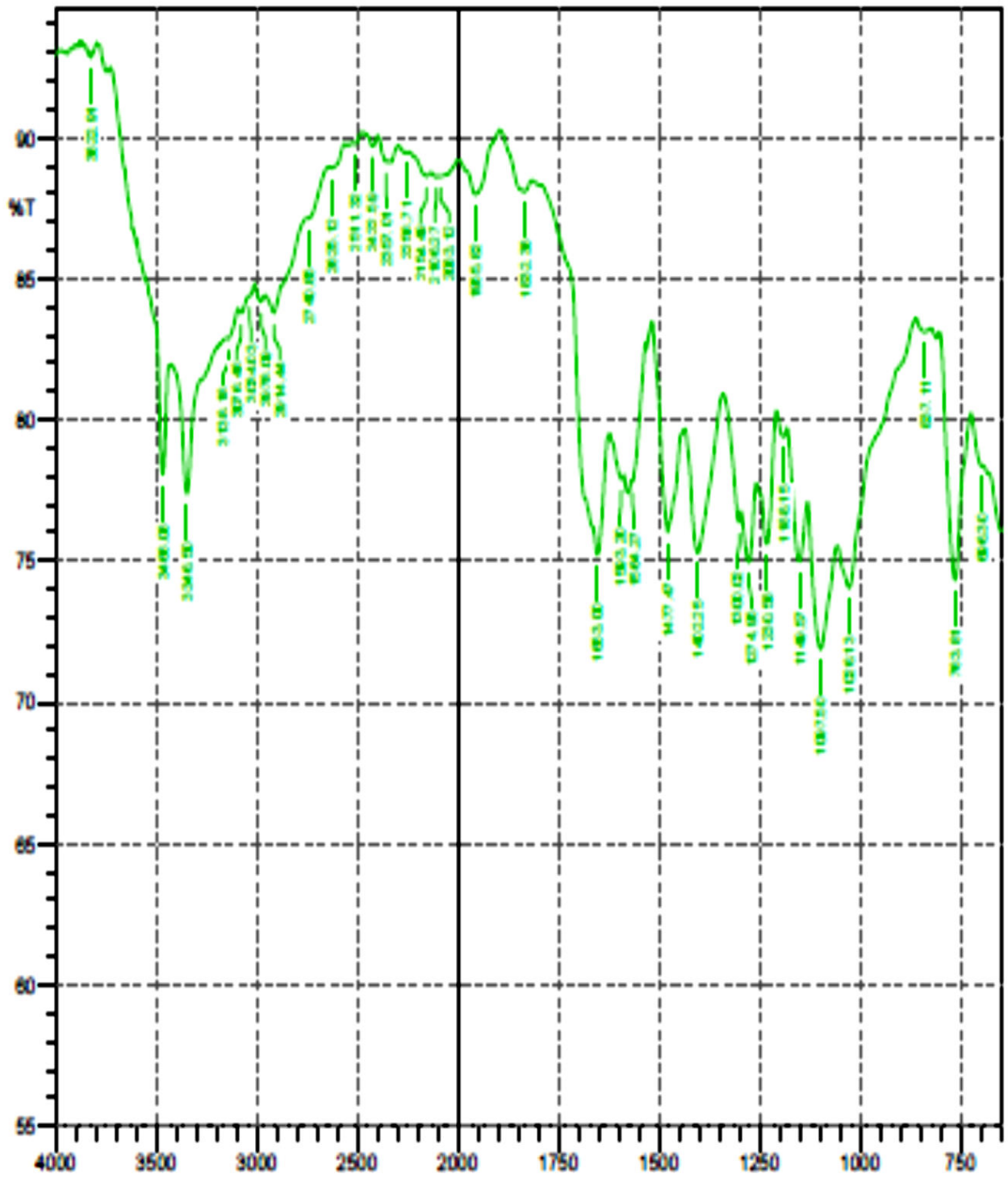


Fig 8: FTIR study of API + METHOCEL K15M PREMIUM

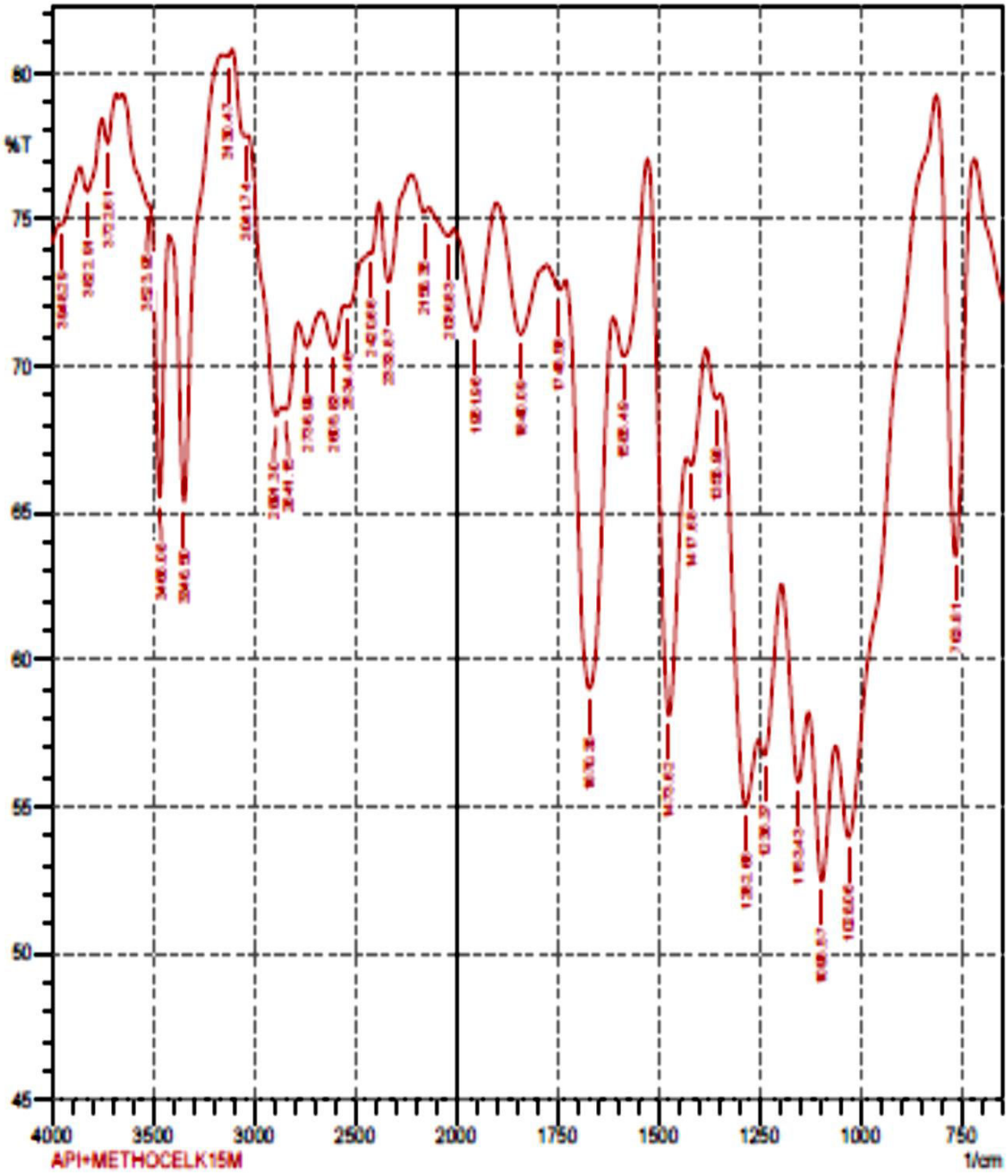


Fig 9: FTIR Study of API+LACTOSE

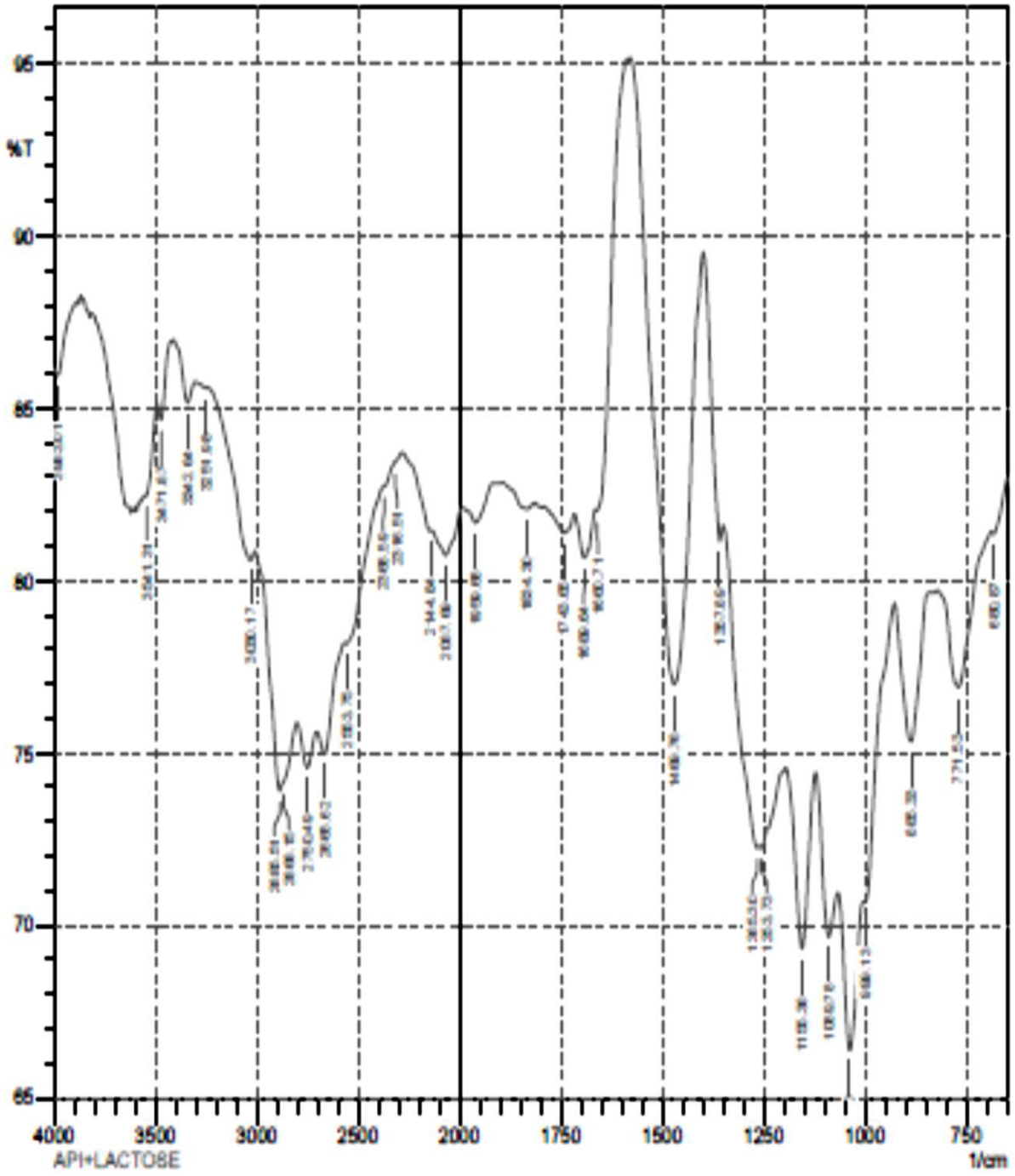


Fig 10: FTIR Study of API+POVIDONE

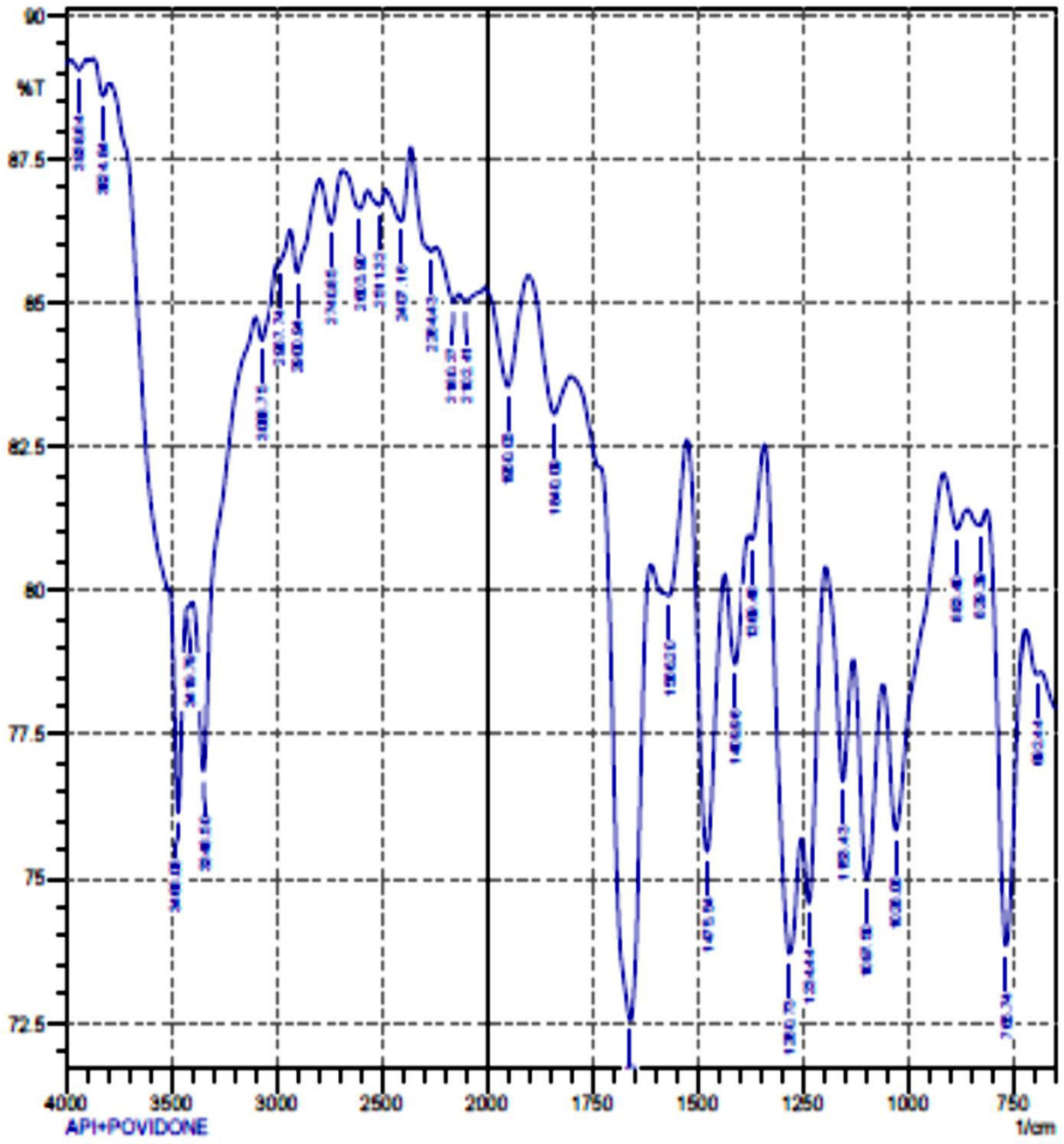


FIG 11: FTIR Study of API+AEROSIL

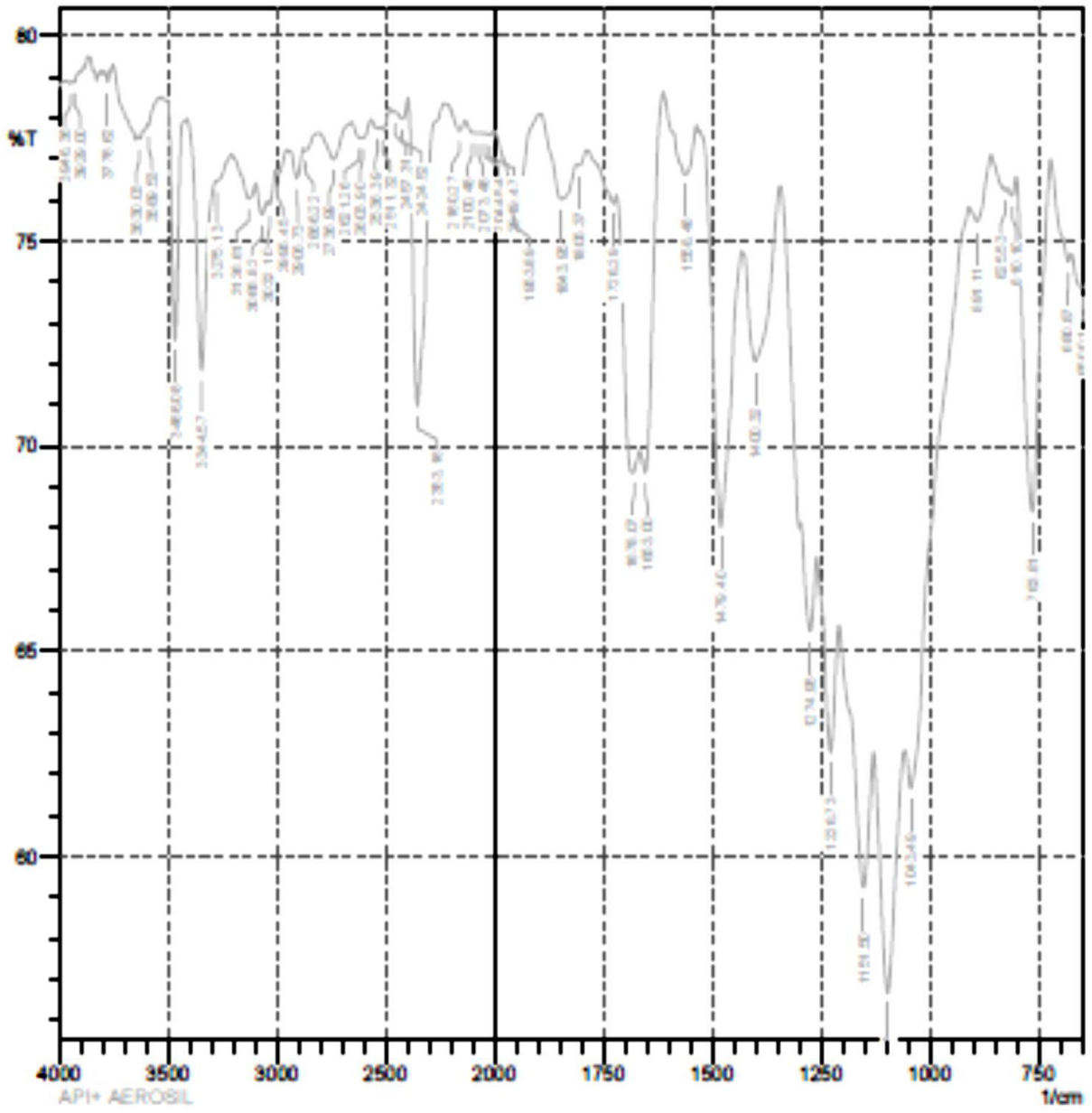


FIG 12: FTIR Study of API+MAGNESIUM STEARATE

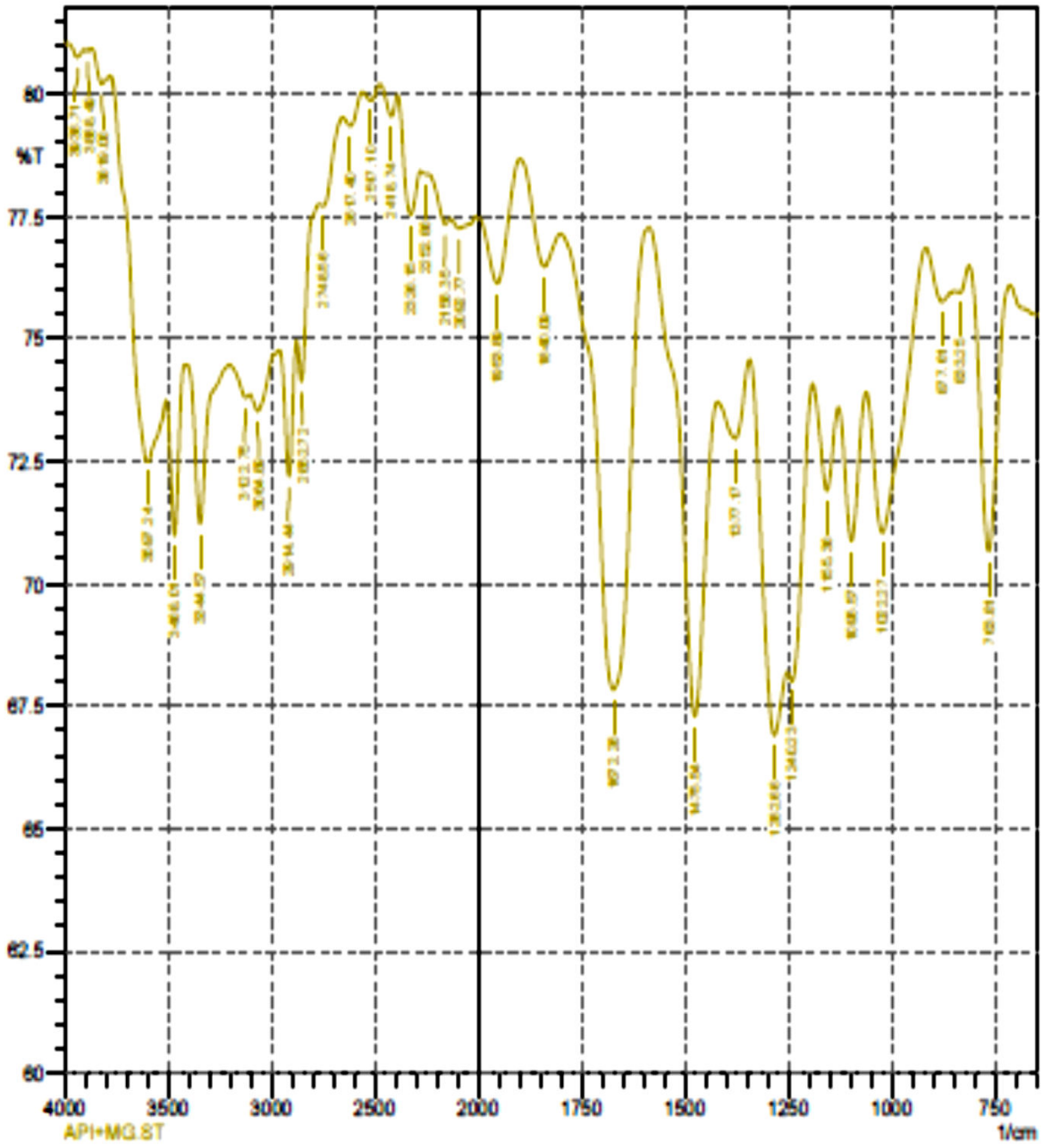
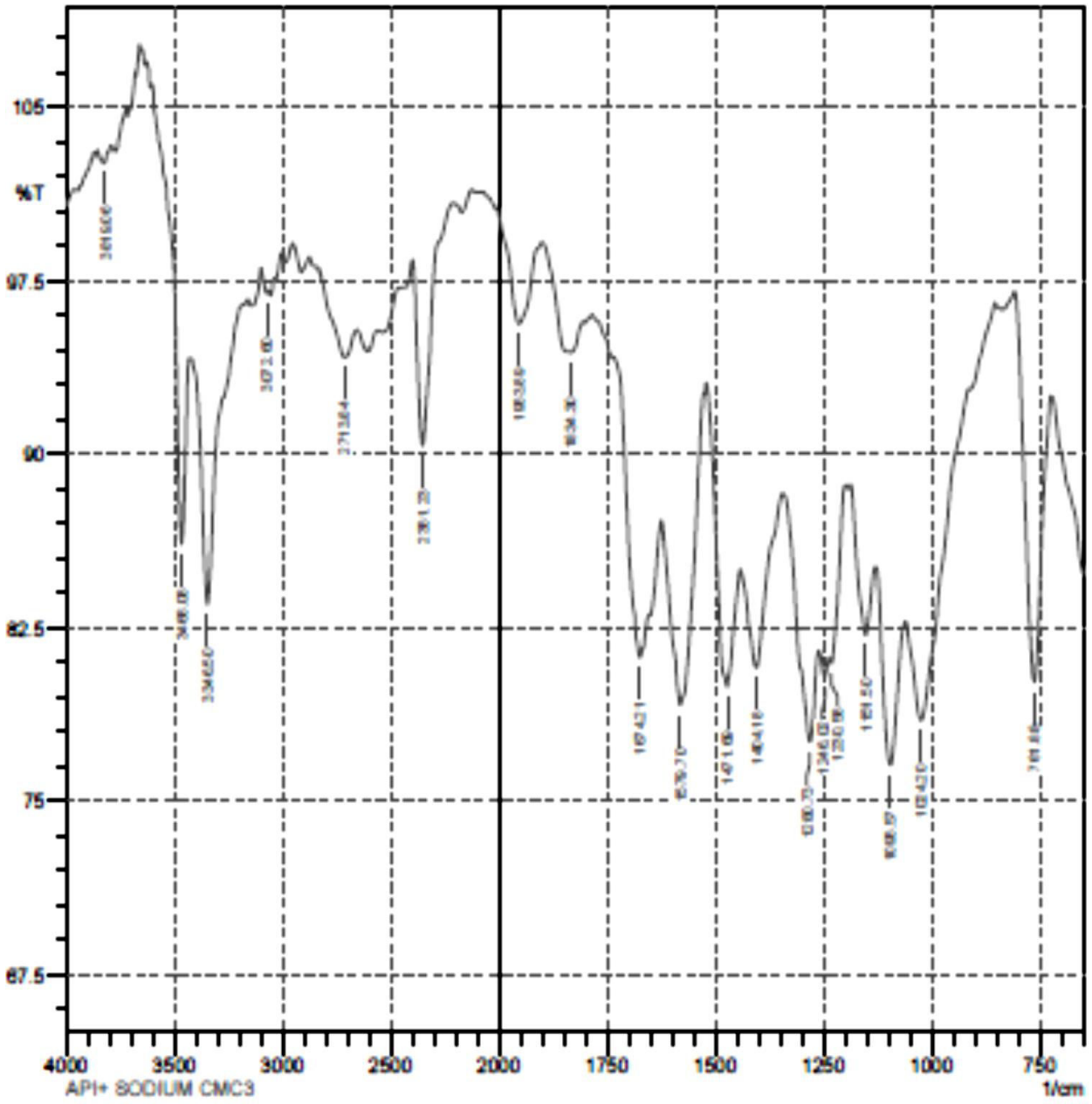


Fig 13: FTIR study of API+CMC sodium



Particulars	Ratio	Description	Parameters				Remarks
			30°C/ 65% RH		40°C/ 75% RH		
			15 days	30 days	15 days	30 days	
API	-	Yellow Powder	No change	No change	No change	No change	Compatible
API: HPMC K15M Premium	1:1	Off white to yellow Powder	No change	No change	No change	No change	Compatible
API: HPMC K4M Premium	1:1	Off white toYellow Powder	No change	No change	No change	No change	Compatible
API: Povidone	1:0.5	Off White to yellow Powder	No change	No change	No change	No change	Compatible
API: Lactose monohydrate	1:5	Off White to Yellow Powder	No Change	No change	No change	No change	Compatible
API: Aerosil	1:0.1	Off White to yellow Powder	No change	No change	No change	No change	Compatible
API: Magnesium stearate	1:0.1	Off White to yellow Powder	No change	No change	No change	No change	Compatible

Table 17: Results of Compatibility studies

Discussion: Pure drug showed characteristic IR absorption bands at 3334 cm-1 for the N-H group bending, 1645 cm-1 for the C=O stretching. The absorption bands at 1556 cm-1 were denoted for stretchingvibrations of C=C in aromatic ring. After analyzing the physical mixtures of API and excipients by FTIR. It was concluded that that there was no interaction between API and excipients.

PRECOMPRESSION EVALUATION

Formulation Code	Bulk density (gm/cm3)	Tapped density (gm/cm3)	Hausner's ratio (HR)	Carr's index (CI)	Angle of repose (θ)
FT-1	0.445	0.608	1.366	26.80	32.06
FT-2	0.458	0.673	1.460	31.95	38.23
FT-3	0.605	0.686	1.13	11.80	45.24
FT-4	0.583	0.652	1.111	10.58	45.06
FT-5	0.508	0.595	1.17	14.62	30.04
FT-6	0.542	0.635	1.170	14.640	32.24

Table 18: Evaluation of micrometrics properties of granules

EVALUATION OF PHYSICAL PARAMETERS OF TABLET

TRIALS	PHYSICAL PARAMETERS			
	Weight variation (mg)	**Hardness** (N)	**Thickness** (mm)	**Friability** (%)
F1	298 ± 5	120± 10	4.21 ± 0.02	0.197
F2	297 ± 5	130± 10	4.20 ± 0.02	0.099
F3	298 ± 5	140± 10	4.20 ± 0.02	0.162
F4	300 ± 5	140± 10	4.18 ± 0.02	0.97
F5	300 ± 5	150± 10	4.19 ± 0.02	0.08
F6	300 ± 5	150± 10	4.19 ± 0.01	0.09

Table 19: Evaluation of Post-Compression properties of Core Tablet

TRIALS	PHYSICAL PARAMETERS		
	Weight variation (mg)	**Hardness** (N)	**Thickness** (mm)
F4	302 ± 5	160± 10	4.22 ± 0.02
F5	303 ± 5	170± 10	4.23 ± 0.02
F6	303 ± 5	170± 10	4.23 ± 0.01

Table 20: Evaluation of Post-Compression properties of Coated Tablets

Discussion:

In all formulations, all physical parameters of tablets within the limits only.

DRUG CONTENT UNIFORMITY

Drug Content Uniformity	F1	F2	F3	F4	F5	F6
API	101	100	99.6	99	100	99.9

Table 21: Evaluation of Drug Content of blend

Discussion:

In all trials, uniformity of content was within the limits i.e. equal proportion of drug content in each tablet.

ASSAY

DRUG CONTENT	F1	F2	F3	F4	F5	F6
API	100.1	99.9	99.9	99.8	100	99.9

Table 22: Evaluation of drug content of ER tablet

IN-VITRO DISSOLUTION STUDY

DISSOLUTION PROFILE OF F1

PERCENTAGE DRUG RELEASE(F1)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
1%w/v SLS medium		**1**	**2**	**3**	**4**	**5**	**6**	
	2	22.3	23.4	22.1	13.0	12.5	23.7	20
	6	84.2	82.6	68.2	70.1	70.4	70.6	74
	12	92.5	81.2	66.6	77.2	100.2	74.4	82

Table 23: Dissolution profile of F1

Discussion:

Under F1 trial, methocel K4M (low viscosity grade polymer) 30mg/tablet and CMC sodium 15mg/tablet was used. At 6th hour, the average drug release was 74% which was not within the limit (30-60%). At 12th hour, the average drug release was 82% which was not under the specified limits (NLT 85%). So the polymer HPMC K4M concentration was slightly reduced in the next trials.

DISSOLUTION PROFILE OF F2

PERCENTAGE DRUG RELEASE(F2)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
1%w/v SLS medium		**1**	**2**	**3**	**4**	**5**	**6**	
	2	17.1	14.5	17.2	15.3	14.5	12.7	15
	6	59.9	60.1	65.0	65.3	75.2	74.8	66
	12	86.1	90.0	84.8	88.0	85.2	87.3	87

Table 24: Dissolution profile of F2

DISSOLUTION PROFILE OF F3

PERCENTAGE DRUG RELEASE(F3)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
1%w/v SLS medium		**1**	**2**	**3**	**4**	**5**	**6**	
	2	15.5	19	18.2	14.1	15.0	14.8	16
	6	65.0	70.0	75.0	74.5	75.5	70.0	70
	12	95.0	92.6	94.0	94.1	69.4	67.4	85

Table 25: Dissolution profile of F3

Discussion:

The average drug release was found to be 66% and 70% respectively in F2 and F3 formula by increasing the quantity of HPMC K4M upto 37.5mg/tablet and CMC sodium concentration was reduced from 15mg to 10mg/tablet. So trial F4 was planned by using HPMC of higher viscosity HPMC K15M.

DISSOLUTION PROFILE OF F4

PERCENTAGE DRUG RELEASE(F4)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
1%w/v SLS medium		**1**	**2**	**3**	**4**	**5**	**6**	
	2	14.0	18.1	13.9	15.1	15.0	15.1	15
	6	31.4	30.6	31.9	27.2	29.0	30.1	30
	12	79.6	80.6	75.1	75.6	80.9	77.8	78

Table 26: Dissolution profile of F4

Discussion:

Under F4 trial, the polymer was changed i.e HPMC K15M which is of high viscosity grade was chosen and CMC sodium was removed. Methocel K15M polymer concentration was about 16.66% (50mg/tablet) which retards the release more. At 6^{th} hour, the average drug release was 30% which is within the lower limit of specification (30-60%). At 12^{th} hour, the average drug release was 78% which was not within the limit (NLT 85%). It means that the drug retards more, so the polymer methocel K15M concentration was reduced in next trial F5.

DISSOLUTION PROFILE OF F5

PERCENTAGE DRUG RELEASE(F5)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
1%w/v SLS medium		**1**	**2**	**3**	**4**	**5**	**6**	
	2	14.0	18.0	15.1	13.9	12.5	12.4	14
	6	39.6	46.1	46.3	39.6	46.0	47.0	44
	12	101	95.0	90.1	87.5	97.5	81	92

Table 27: Dissolution profile of F5

Discussion:

F5 formula, the polymer methocel K15M concentration was reduced to 11.66% (35mg/tablet). It increased the release at 6th hour to an average of 44% which is within the limit of 30-60%. The second hour release was found to be 14% which is within the limit of NMT 30%. At 12th hour release was found to be 92% which is above the limit of NLT 85%.

Drug release was achieved as per the specifications designed for dissolution testing, so next reproducible trial to be planned and to check and confirm the drug release as per formula F5.

DISSOLUTION PROFILE OF F6

PERCENTAGE DRUG RELEASE(F6)								
MEDIUM	**TIME**	**UNIT**						**Avg%**
1%w/v SLS medium		**1**	**2**	**3**	**4**	**5**	**6**	
	2	11.2	17.8	9.2	6.4	11.7	15.1	12
	6	38.3	57.8	35.7	29.0	41.1	49.9	42
	12	81.5	101.0	81.7	90.5	86.5	97.9	88

Table 28: Dissolution profile of F6

Discussion:

The drug release of F6 trial is reproducible as F5 formula. So F5 formula was finalized as final prototype formula for the extended release formulation.

COMPARATIVE INVITRO DISSOLUTION PROFILE FROM F1-F6

TIME(HOURS)	% CUMULATIVE DRUG RELEASE						SPECIFICATIONS
	Average % drug release for all trials						
	F1	F2	F3	F4	F5	F6	
2hr	20	15	16	15	14	12	NMT 30%
6hr	74	66	70	30	44	42	30-60%
12hr	82	87	84	78	92	88	NLT 85%

Table 29: Comparative invitro dissolution profile from F1-F6

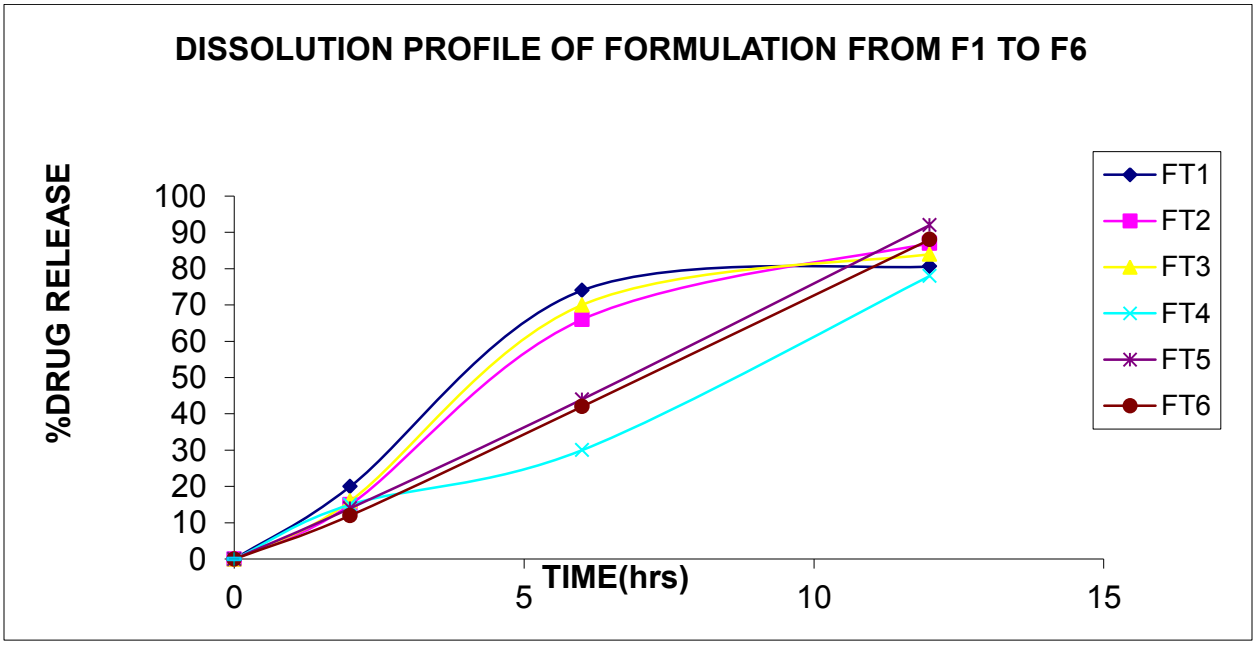


Fig 14: Comparitive dissolution profile from F1 to F6

DATA ANALYSIS

Kinetic study:

Formulation-5 was found to be the desired *In-vitro* dissolution rate, so this formulation was selected for determining the nature of drug release from dosage form.

Time (in hours)	Square root of time	Log Time	% CDR	Log(100 % - CDR)	Log %CDR
2	1.414213562	1.411	14	1.99492	1.146128036
6	2.449489743	2.44	44	1.99280	1.643452676
12	3.464101615	3.46	92	1.99138	1.963787827

Table 30: Different Kinetic models

Formulation	Zero-order kinetics	First-order kinetics	Higuchi's kinetics	Korsmeyer-Peppas
F5	**0.912**	**1**	**0.981**	**0.986**

Table 31: Regression coefficients from all the Kinetic model graphs

KINETIC MODELS

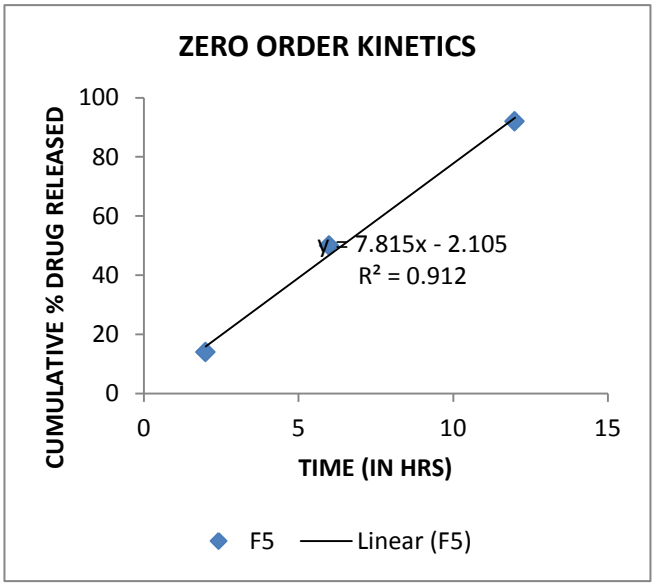


Fig 15: Zero order kinetics

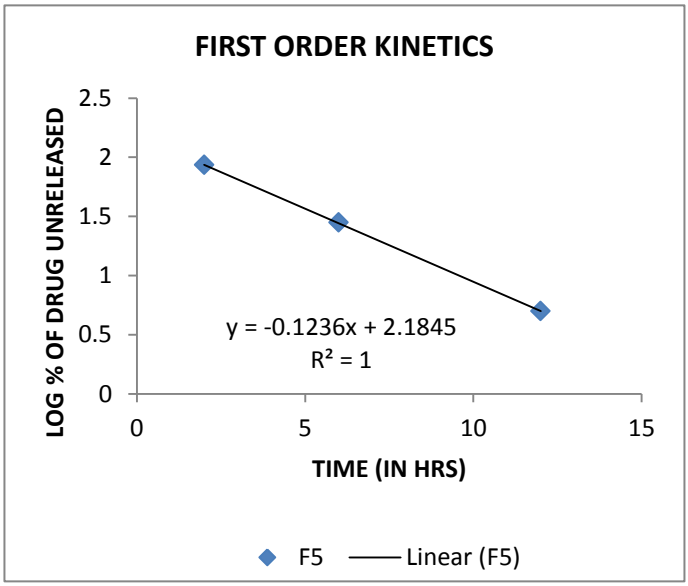


Fig16:First order kinetics

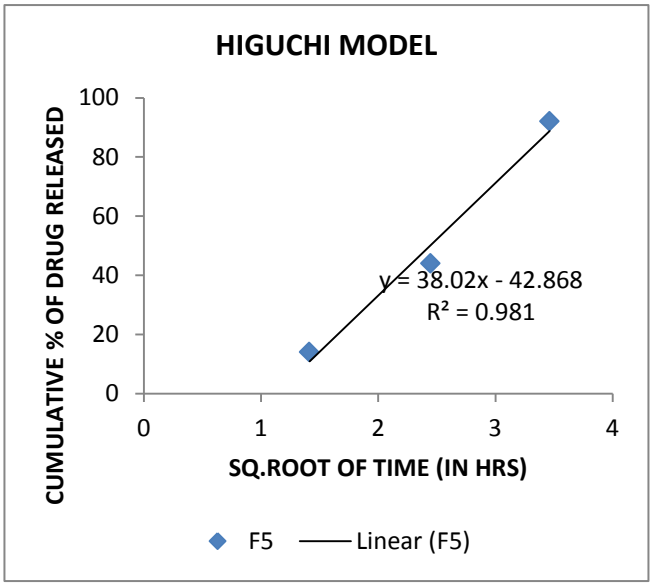


Fig 17: Higuchi model

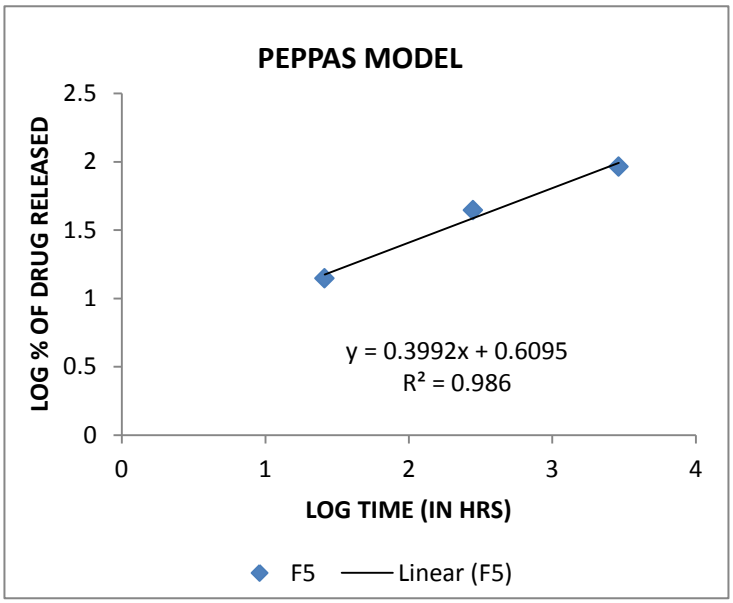


Fig 18:Peppas model

Discussion:

The curve fitting results of the release rate profile of the designed formulations gave an idea on the mechanism of drug release.

Based on the data analysis, it was found that the drug release follows First order release kinetics, as it showed the highest linearity and concluded that the release mechanism was matrix diffusion controlled.

9. SUMMARY

In the study, anticonvulsant drug was selected for designing extended release matrix tablets. Pre-formulation studies were done with API. Compatibility was done before choosing the excipients for the study with physical observation and FTIR studies. The samples were charged in stability chambers at conditions 30°C/65%RH and 40°C/75%RH for 30 days. All the pre-formulation studies and compatibility studies were found to be satisfactory. So formulation trials were followed with the selected excipients.

Blend for ER formulation was prepared by wet granulation method. Hypromellose K4M and Hypromellose K15M were used as release retarding polymers for optimizing the formula.

Six trials were taken to optimize the release of API in ER form to be within specifications. F5 is the optimized formula with 11.66% concentration of HPMC K15M polymer which optimized the drug release profile as per predetermined specifications. A reproducibility trial F6 was performed to check the reproducibility of process of drug release as per F5.

For the ER form, Other excipients include povidone as binder, Lactose monohydrate as diluent, colloidal silicon dioxide as glidant and Magnesium stearate as Lubricant. Instacoat yellow was used as ready mix.

Post-Compression analysis of all formulations like Hardness, Weight variation, Friability and Assay were within the limits for all the formulations. *In-vitro* dissolution studies were performed by HPLC method revealed that the formulation F5 released the drug as per the specifications. Kinetic Model fitting was done by plotting graphs for Zero-Order kinetics, First-Order kinetics, Higuchi's Kinetic model and Korsemeyer - Peppas kinetic model. The formulation selected was F5 which has shown the release rate of the drug by First order kinetics and follows matrix diffusion controlled mechanism. Accelerated stability studies are being performed.

10. CONCLUSION

The aim of the study is to design and develop extended release matrix tablets of anticonvulsant drugs. Hypromellose, water swellable polymer was selected for the extended release of API.

The formulation was optimized to obtain the release of API for a sustained period of 12 hours. In the initial trials, Hypromellose K4M of low viscosity grade was used, and then Hypromellose K15M of high viscosity grade was selected to check the feasibility of the polymer to sustain the release of API. With HPMC K4M the drug release was not controlled to the desired limit of 30-60% at 6^{th} hour. So, a still high viscous polymer Hypromellose K15M was used in the formulations F-4 to F-6. The incorporation of the Polymer intra-granularly at concentration 11.66% gave an optimum release profile within specifications.

From graphs plotted for various Kinetic models, it can be concluded that the F5 follows First-order kinetics as the plots of that model had shown higher regression value. F5 formula extended the release and follows matrix diffusion controlled mechanism.

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